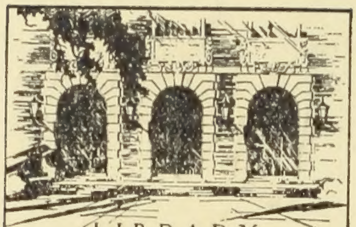

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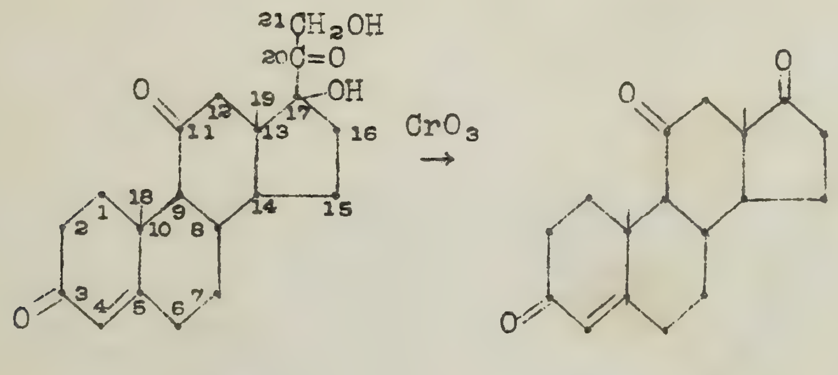
CORTISONE (KENDALL'S COMPOUND E)

Reported by Robert L. Frank September 30, 1949

Introduction.--In the spring of this year there was announced from the Mayo Clinic (1) the discovery that 17-hydroxy-11-dehydrocorticosterone (I) (3,11,20-triketo-17(beta),21-dihydroxy-Δ^4-pregnene; Kendall's Compound E; Wintersteiner's Compound F; Reichstein's Compound Fa; and now designated cortisone), one of the steroid hormones of the adrenal cortex gland, will rapidly relieve the symptoms of rheumatoid arthritis and (perhaps) other rheumatic diseases. The spectacular effects of the treatment, especially in view of the wide occurrence and crippling nature of arthritis, have attracted immediate popular acclaim, even though the hormone is not without side effects and the results of its continued use are not yet known (2,3,4).

Isolation and Proof of Structure.--The first crystalline material from the suprarenal cortex was extracted by use of acetone and benzene in December, 1933, by Mason, Myers, and Kendall (5). This was part of a mixture from which have since been isolated, mainly by means of Girard reagents and chromatography, upwards of nineteen steroidal components (6,7). One compound with cortical activity was designated Compound E (6), and later shown to be identical with Compound F of Wintersteiner and Pfiffner (8) and Compound Fa of Reichstein (9). Its structure (I) was elucidated between 1936 and 1938 through the combined work of the Mayo group (6,7,10,11) and Reichstein and his coworkers at the University of Basel in Switzerland (9,12,13,14).

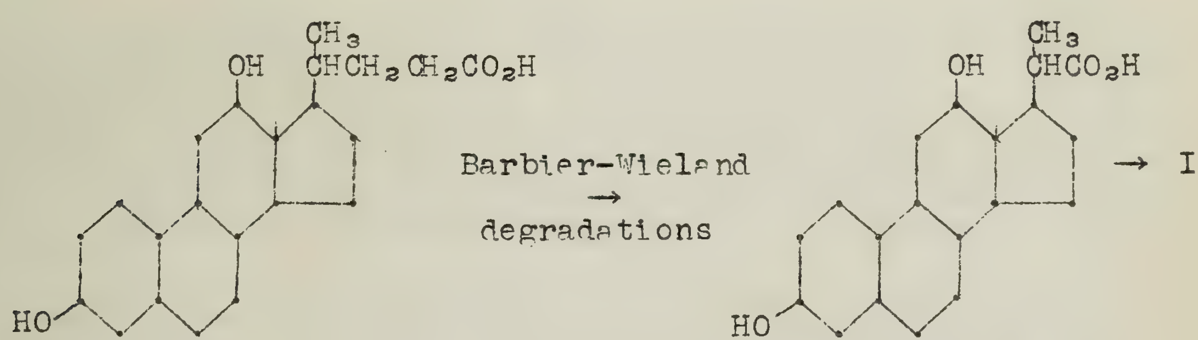


I II

The important points of the structure proof are as follows:
1. Chromic acid oxidation converted cortisone (I), $C_{21}H_{28}O_5$, to a triketone, adrenosterone (II), $C_{19}H_{24}O_3$, indicating the loss of a two-carbon side-chain having two oxygen atoms, and also indicating the position of the tertiary hydroxyl group.
2. Periodic acid oxidation suggested the nature of the side chain ($-COCH_2OH$) by forming an acid, $C_{20}H_{26}O_5$, and formaldehyde.
3. Weak androgenic hormone activity of the triketone adrenosterone (II) suggested its structural similarity to the male hormone androsterone (3(alpha)-hydroxy-17-keto-etioallocholane), the structure of which was already known. The carbon skeleton of this triketone was subsequently confirmed by catalytic reduction of

the double bond followed by Clemmensen reduction to the previously known androstane.
4. The location of two of the carbonyl groups of the triketone II at C_3 and C_{17} was shown by interrelation with other hormones, some of which had been converted to the known 3,17-androstanediol.
5. The remaining carbonyl group was assigned to position 11 or 12 by elimination of other possible positions and by virtue of its lack of reactivity. Position 12 was later eliminated by Mason and Hoehn by comparison of cortisone oxidation products with the similar compounds from bile acids having a proven carbonyl at position 12.

Synthesis of Cortisone from Desoxycholic Acid from Bile.--A thirty-seven step synthesis of cortisone from desoxycholic acid (III), based partly on previous work of Hoehn and Mason (15), has been reported by Sarett of Merck and Company (16) (over-all yield ca. 0.05%):

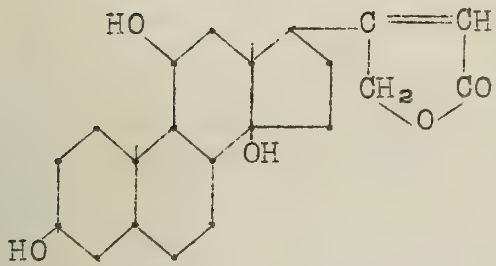


III IV

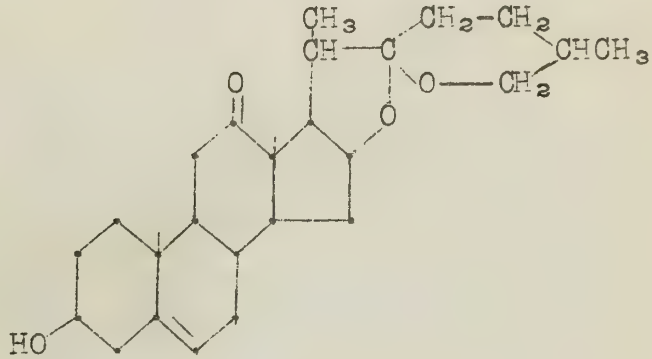
The essential stages of the synthesis from bis-nor-desoxycholic acid (IV) involve (a) replacement of the hydroxyl at C_{12} by a carbonyl at C_{11} by dehydration, hypohalogenation, oxidation, and dehalogenation; (b) replacement of the side chain at C_{17} by an oxygen atom by reaction with hydrazoic acid to replace the 20-carboxyl group by an amino group, reaction with nitrous acid, dehydration, and ozonolysis; (c) introduction of the proper C_{17} side chain by use of acetylene, reduction and bromination steps, and osmium tetroxide and chromic acid oxidations; and (d) introduction of the Δ^4 double bond by reaction of bromine followed by pyridine.

Other Synthetic Possibilities for Cortisone and Its Analogs.--Two plant steroids have been suggested as starting materials for cortisone synthesis, and their structures below indicate their potentialities. One is sarmentogenin (V), which occurs as a glycoside in the seeds of *Strophanthus sarmentosus*, an African vine (17). The structure of sarmentogenin is certain except for the position of the tertiary hydroxyl group (tentatively at C_{14}) and Katz (18) has recently proven the C_{11} location of one hydroxyl group. The other is botogenin from the Mexican plant *Dioscorea*

mexicana (19), the structure (VI) of which has been assigned by Marker and coworkers (20), although not rigorously proven.



V



VI

The stereochemical relationship of these steroids with cortisone has not been established, but the preponderance of keto groups and the Δ^4 unsaturation of cortisone reduce the stereochemical problems to a minimum. The carbon skeletons of nearly all the natural steroids have been found to differ only in reference to the groups around C_5 (21), and there is every likelihood that the above compounds are theoretically capable of being converted to cortisone.

Many further synthetic schemes will probably develop during the coming months. For example, one recent communication (22) describes a means of introducing a 17-hydroxyl group into 11,20-diketo steroids by use of perbenzoic acid.

Medical interest has also been shown in the 11-desoxy analog of cortisone (Reichstein's Compound S (23)).

Adrenocorticotropic Hormone (ACTH).--Mention should be made of the fact that the anti-arthritic effects of cortisone can also be achieved by use of the polypeptide adrenocorticotropic hormone of the anterior lobe of the pituitary gland (1). This material has previously been known to stimulate the output of the adrenal glands, and its manufacture is under development, notably by Armour and Company.

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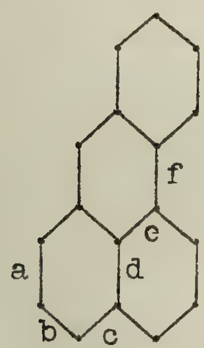
MATRINE

Reported by Nelson J. Leonard September 30, 1949

Matrine, one of the lupin alkaloids, was first isolated by Nagai, who also assigned the correct molecular formula, $C_{15}H_{24}N_2O$. The alkaloid exhibits polymorphism, and some of the forms have been interconverted. Although the structure of matrine has not been thoroughly established, the structural representation which is deemed most satisfactory by the Japanese investigators, who have done most of the work on matrine, has been given as I by Tsuda. Matrine is thus similar in ring system to perhydrobenz[de]anthracene (II), and it is similar in constitution to the more completely characterized lupin alkaloid, lupanine (III). The suggested grouping is unusual



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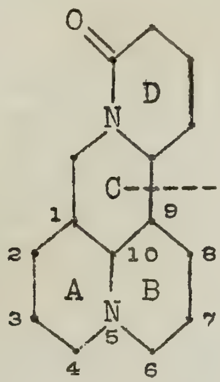
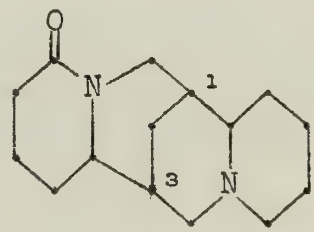


I



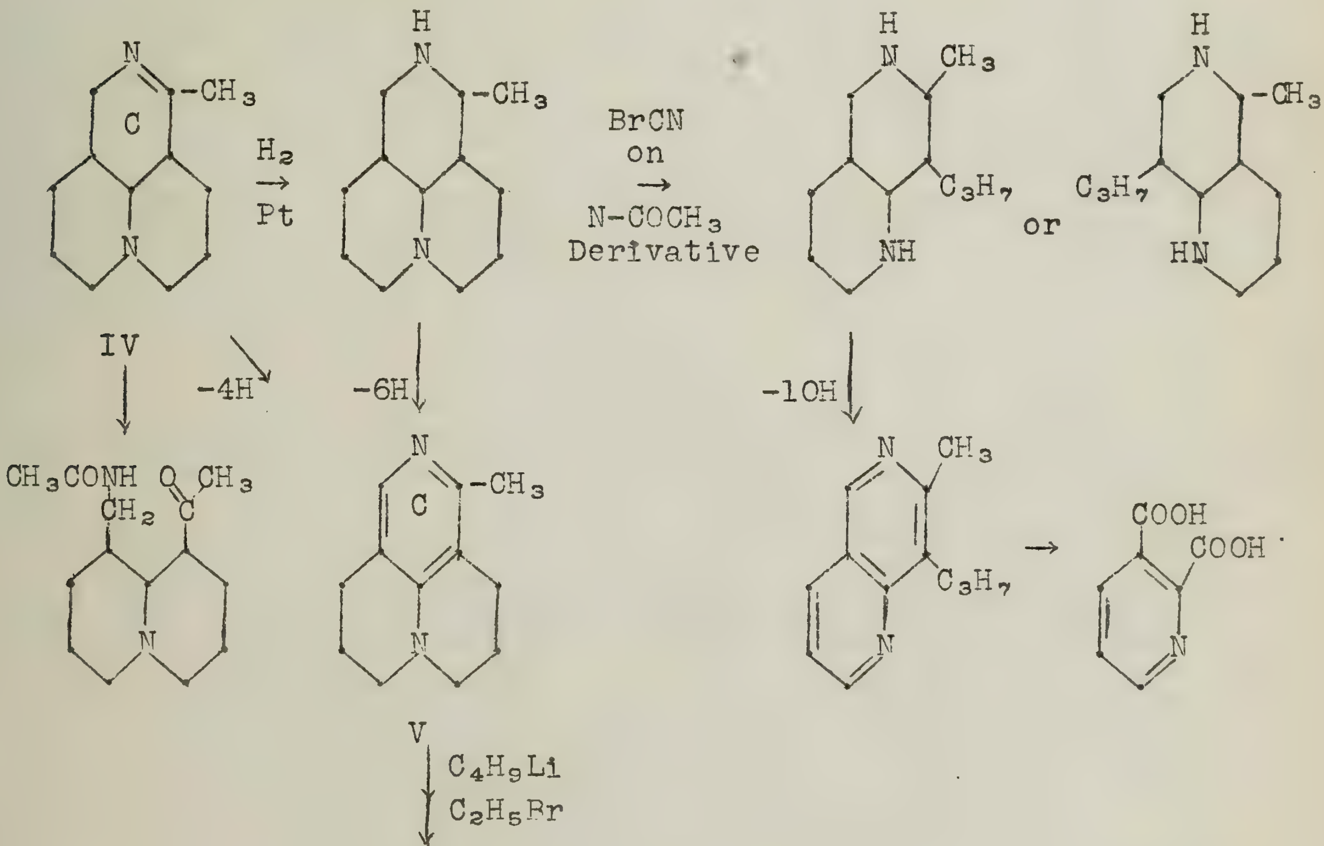
III

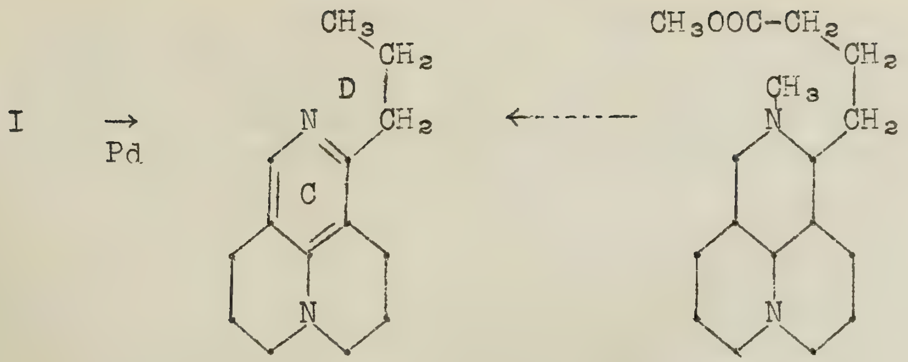
for the lupin alkaloids, since in lupanine and most of the other C_{15} compounds, the third and fourth rings are created by junction at the 1- and 3-positions of quinolizidine (rings A and B, unsubstituted). In the proposed formula for matrine, by contrast, the third and fourth rings are created by junction at the 1- and 9-positions of the quinolizidine portion.

The nature of the two nitrogen atoms present in matrine was revealed by the absence of imino and N-methyl groups, the behavior of the alkaloid as a monoacidic base, and its hydrolysis in ethanolic potassium hydroxide to give potassium matrinate, $C_{15}H_{25}N_2O_2K$. The corresponding amino acid, matrinic acid, was liberated from the potassium salt by treatment with ammonia, and the presence of a newly formed secondary nitrogen was indicated by the positive Liebermann nitroso reaction. Matrinic acid was reconverted to matrine by means of heat. Therefore, each of the nitrogens was indicated as tertiary and common to two rings, with one present in a lactam grouping. The product resulting from the sodium and amyl alcohol reduction of matrine was not well defined, but the zinc dust distillation of matrinic acid hydrochloride produced a small amount of an isomer of sparteine, $C_{15}H_{26}N_2$, corresponding to the completely reduced ring system.

The nature of rings A and B in matrine (I) was indicated mainly by soda-lime distillation and by zinc dust distillation experiments. Thus, matrinic acid hydrochloride gave, among other products of zinc dust distillation, an optically inactive tertiary base, $C_{10}H_{19}N$. Winterfeld and Kneuer proved, by direct comparison with an authentic sample, that the $C_{10}H_{19}N$ base was 1-methylquinolizidine. The soda-lime distillation of potassium matrinate produced a fraction which was hydrogenated catalytically to a mixture of quinolizidine and α-n-butylpiperidine. Both components were carefully identified. The formation, indirectly from matrine, of 1-methylquinolizidine, quinolizidine, and α-n-butylpiperidine accounted for rings A and B of matrine (I) with at least one carbon atom attached to the quinolizidine portion, and at C_1.

The nature and location of ring C in matrine were more difficult to ascertain, but again rather drastic degradation experiments provided the clues. Soda-lime distillation of potassium matrinate gave two C_{12} products, α-matrinidine, $C_{12}H_{20}N_2$ (IV) and optically inactive β-matrinidine, $C_{12}H_{16}N_2$ (V), and these bases were interrelated and characterized further as outlined below:





VI VII

The presence of an active methyl group in β-matrinidine (V) was indicated by its formation of a benzal derivative and a lithium derivative. Condensation of the lithium derivative of V with ethyl bromide furnished a $C_{14}H_{20}N_2$ product (VI) identical with that obtained by dehydrogenation of matrine (I) over palladium on asbestos at 300°. In the dehydrogenation of matrine an octadehydromatrine, $C_{15}H_{26}N_2O$, was also formed. The behavior of this compound as a typical α-pyridone contributed further towards a decision as to the nature of ring D. The degradation of the carbomethoxyl group of methyl methylmatrinate (VII) - by means of the Hofmann or Curtius method - eventually to hydrogen produced a $C_{14}H_{26}N_2$ molecule, "descarbonylmatrinane". Dehydrogenation of this over palladized asbestos gave $C_{14}H_{20}N_2$, identical with VI. This study and further oxidation studies appear to establish ring D in matrine as a piperidone ring and therefore to indicate the total structure of the alkaloid as I.

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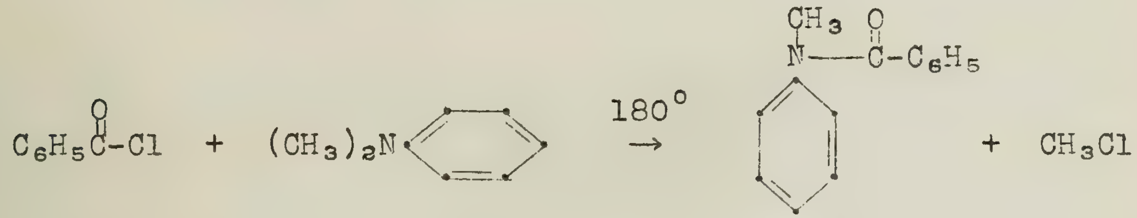
INTRAMOLECULAR REACTION OF ACID CHLORIDE AND TERTIARY AMINO GROUPS (5)

Reported by S. M. Cohen   October 7, 1949

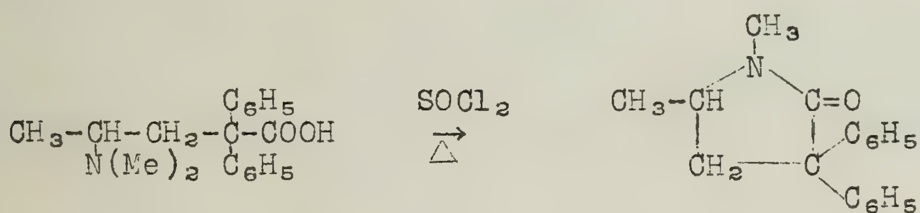
The following reactions of tertiary amines and acid chlorides or bromocyanogen, with elimination of a mole equivalent of alkyl halide, are well known.



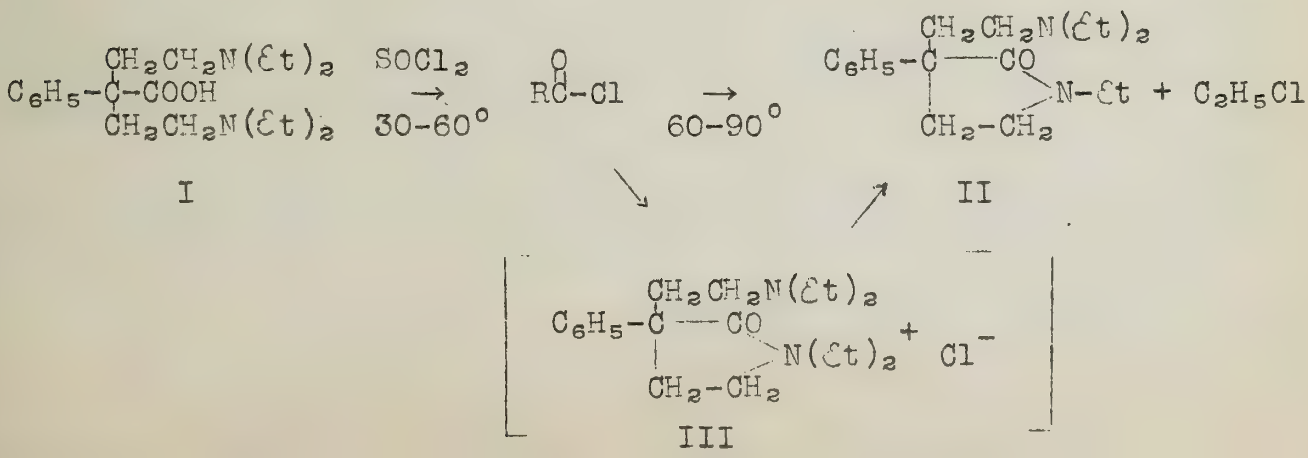
(1)

$$R_3N + Br{-}CN \rightarrow R_3\overset{+}{N}{-}C{\equiv}N\ \ Br^- \rightarrow R_2N{-}CN + RBr \qquad (2)$$

In a recent paper (4) reporting some new compounds related to "methadone", it was noted that several compounds of the type γ-dimethylamino-α,α-diphenylvaleric acid were converted, on refluxing with thionyl chloride, to the corresponding pyrrolidone, as exemplified below.



Further studies (5) indicated that α,α-bis-(diethylaminoethyl)-phenylacetic acid (I), with thionyl chloride, resulted in formation of 1-ethyl-3-(β-diethylaminoethyl)-3-phenyl-2-pyrrolidone (II) and ethyl chloride. As an intermediate, the formation of a transitory quaternary amide form (III) was postulated.

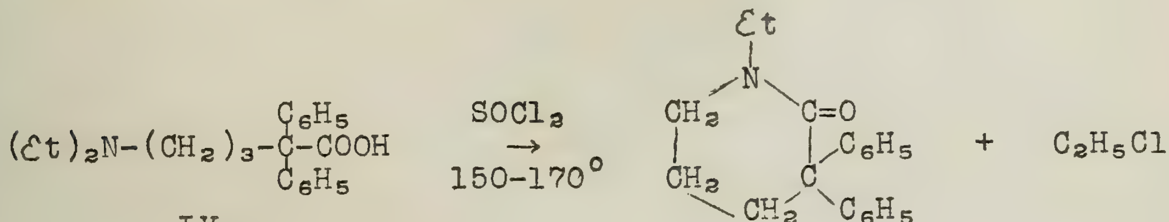


I II III

In this type reaction, cleavage of various alkyl groups from the nitrogen has been found to favor elimination of the smaller group.

This type of reaction, where a molecular equivalent of alkyl halide is eliminated, has been found to be applicable to a wide variety of compounds. Therefore the reaction can be classed as "general".

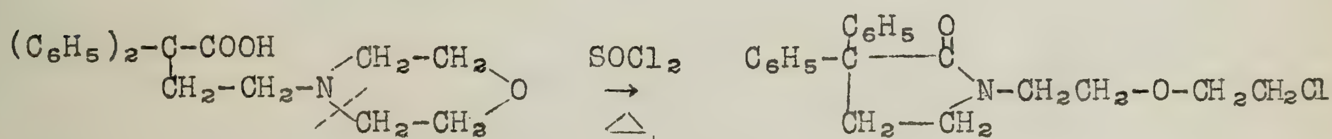
Thus, a six-membered ring, a piperidone, is formed from δ-dialkylamino-α,α-diphenylvaleric acid (IV).



IV

It should be noted tha an elevation in temperature 70-90° above that required to close a five-membered ring is required to close the corresponding six-membered ring.

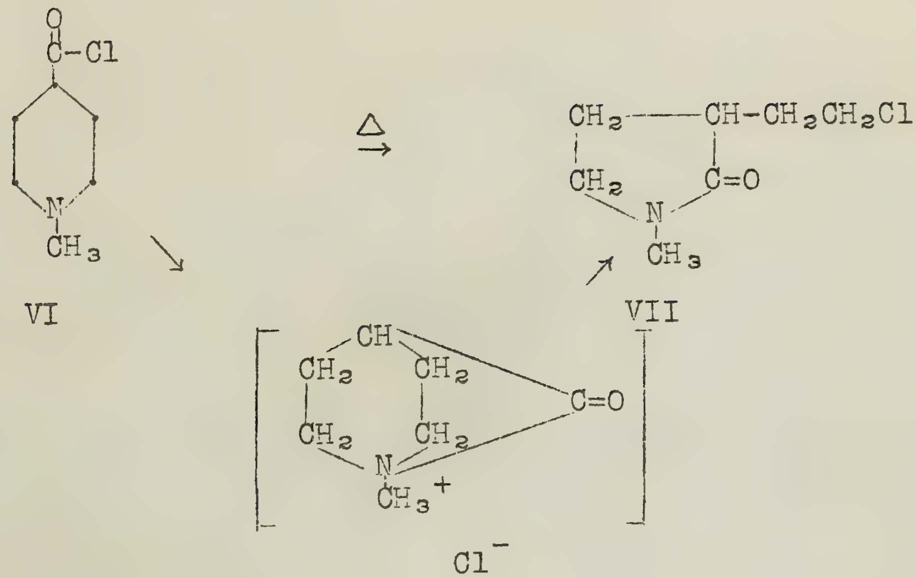
This elimination of an alkyl halide in these reactions lead to a study of substances containing a heterocyclic ring-nitrogen. It was postulated that cleavage of the carbon-nitrogen bond might result in cleavage of this ring and retention of the halogen in the molecule. Among the compounds studied was γ-morpholinyl-α,α-diphenylbutyric acid (V).



V

Also tested in this reaction were γ-pyrrolidyl- and γ-piperidyl-α,α-diphenylbutyric acids. In each case, the ring was opened to give an ω-chloroalkyl side-chain attached to the nitrogen atom of the pyrrolidone produced.

In a variation of this reaction, 1-methylpiperidine-4-carboxylic acid chloride (VI) yielded the compound 1-methyl-3-β-chloroethyl-2-pyrrolidone (VII).



VI VII

Since cleavage of the smallest alkyl group is usually expected, it would be expected, in this last example, that elimination of the methyl group would occur. Apparently, however, the strain imposed by closure of the pyrrolidone ring caused preferential cleavage of the existing ring at the carbon-nitrogen bond.

In forming the acid chlorides of the tertiary amino acids, thionyl chloride or phosphorus trichloride was found to be a satisfactory reagent. The latter was suitable when the former was not.

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A RECENT EXTENSION OF BREDT'S RULE

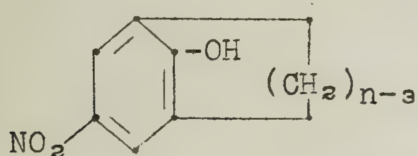
Reported by Emil W. Grieshaber October 7, 1949

In 1918 Bredt made the following generalization: "In the bicyclic [3,3,1] and [2,2,1] type of molecule a double bond cannot occur at a bridgehead carbon." Although his earliest reference to such a concept had been published in 1902 it was not until 1921 that the term "Bredt's Rule" appeared in the literature (1,2). From the start considerable criticism has appeared in the literature regarding the applicability and validity of this rule. Perhaps the main cause of this controversy is overgeneralization of the rule. Many workers have attempted to apply it to bicyclic systems different from those originally specified.

One of the most resourceful and original critics of this rule is the Swiss chemist Prelog. Within the past few years he and his coworkers have synthesized two different series of compounds both of which, he claimed, violate Bredt's rule.

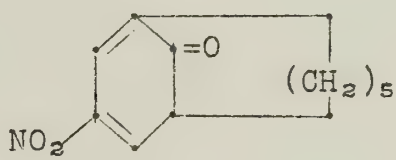
I

One of these is a series of benzopolymethylene compounds represented by formula I (3). A study of various physical properties (u.v. absorption, acidity of phenol) led him to the conclusion that when (n-3) = 5, (i.e. an 8-membered ring) the compound existed in the keto form (II) with the planar ring distorted and with its aromaticity destroyed. Compound II contains a bridgehead double bond.



(n-3) = 5-15,17,18,27

I



[5,3,1]

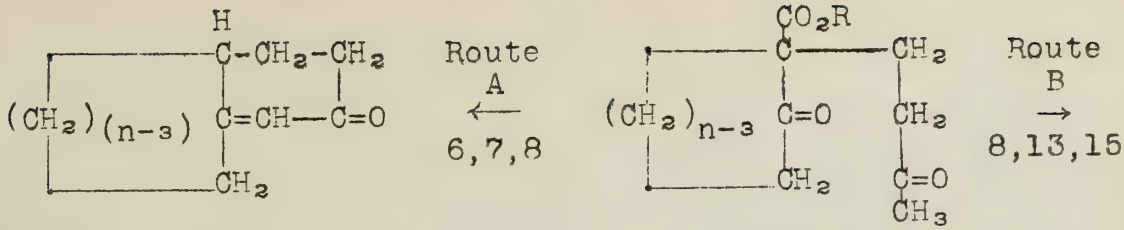
II

(1)

These data would therefore establish the fact that for the bicyclic [3,1,5] undecane Bredt's rule definitely does not hold true. Nothing can be said conclusively about the [3,1,4] system from the above.

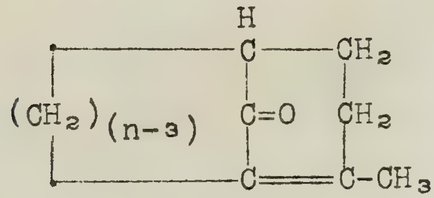
II

In his most recently published works Prelog (4,5,6) described a second series of bicyclic compounds which violate his interpretation of Bredt's rule. These compounds are similar to either a bicyclic [4,0,X] alkene (IV) or a bicyclic [3,1,X] alkene (V).



IV [4,0,X] III

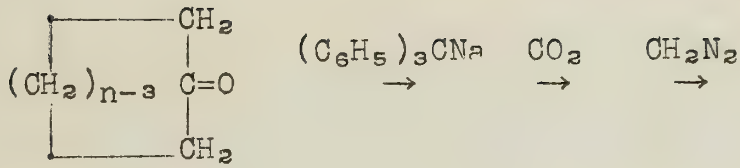
(2)



V [3,1,X]

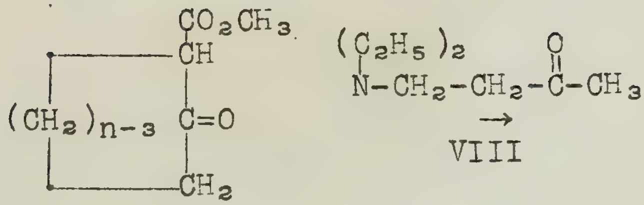
From these equations it may be observed that compound III may condense in either of two ways - route A or B - depending on the size of the cyclic ketone. Prelog claimed that both IV and V violate Bredt's rule. However, his data establish the applicability of Bredt's rule to the bicyclic system [3,1,4]. This is done by reasoning as follows: Route B was not taken when $n < 8$ (i.e. $X < 5$) therefore the bicyclic system [3,1,X] (V) is unstable or cannot be formed for values of X less than five. In other words, Bredt's rule may be considered valid for the bicyclic system [3,1,4]. Since earlier work left this case in doubt the present work is very significant. His data also show conclusively that the rule does not hold for the bicyclic [4,0,4] (IV) system since here a double bond actually does exist at a bridgehead.

The chemistry involved in the synthesis of compound III above and the methods employed in determining the structural differences of IV and V is of interest. The sodio derivative of a given cyclic ketone was prepared by treating the ketone with triphenylmethylsodium. Subsequent addition of carbon dioxide followed by treatment with diazomethane yielded the desired α-carbomethoxy cyclic ketone, (VII). The doubly activated α-hydrogen remaining was replaced by a 2-butanone fragment by condensing VII with the quaternary base N,N-diethyl-2-butanone methiodide (VIII) according to a procedure described by Wilds and Shunk (7) to give III. This could be saponified and decarboxylated under mildly acidic conditions followed by condensation along either route A or B above by employing sodium methoxide as catalyst.



VI

(3)



VIII III

VII

In the case of cyclooöctanone, mixtures of IV and V were obtained. Separation was effected by chromatographic adsorption.

Several differences in properties of IV and V aided in establishing their structures. IV reacted readily with carbonyl reagents, whereas V was unaffected under the same conditions. IV when subjected to a Kuhn-Roth determination gave no acetic acid; V gave one mole of the acid, indicating one $=C-CH_3$ grouping. The ultra-violet absorption curves for IV and V differed from each other but each agreed with curves of other compounds within the respective series and also with related compounds of established structure.

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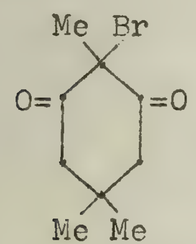
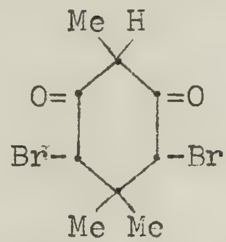
MIGRATION OF BROMINE IN β-KETOESTERS AND 1,3-DIKETONES

Reported by Allen B. Simon — October 7, 1949

Hantzsch (1) was the first to observe that upon bromination of ethyl acetoacetate, ethyl-α-bromoacetoacetate is initially formed but then is quickly converted into ethyl-γ-bromoacetoacetate in the presence of the hydrogen bromide which is produced.

$$CH_3COCH_2COOEt + Br_2 \xrightarrow{AcOH} CH_3COCHBrCOOEt + HBr$$
$$\downarrow$$
$$BrCH_2COCH_2COOEt$$

This α → γ migration has been observed only with bromine; chlorine gives the α-chloro compound. In the past the following compounds, all either β-ketoesters or 1,3-diketones, have been shown to undergo the migration

Compounds	Products	Ref.
CH_3COCH_2COOEt	$BrCH_2COCH_2COOEt$	1
$CH_3COCH_2COCH_3$	polybromo compounds	2
$CH_3COCHCH_2COOEt$ (COOEt)	$BrCH_2COCHCH_2COOEt$ (COOEt)	3
$CH_3COCHCOOEt$ / $CH_3COCHCOOEt$	$BrCH_2COCHCOOEt$ / $BrCH_2COCHCOOEt$	3
$C_6H_5COCH_2COCH_3$	$C_6H_5COCH_2COCH_2Br$	4
		5

Recently Becker (6,7) undertook a continuation of the study of the reaction. He has shown that two bromine atoms can successively migrate. Bromination of an acetone solution of ethyl diacetylacetate (I) gave ethyl-γ, γ'-dibromodiacetylacetate (II). The structure of (II) was established by comparison with the product of an unequivocal synthesis.

Bromination and subsequent rearrangement should occur with substituted ethyl diacetylacetates and related compounds to yield γ-bromo derivatives. However, an ether solution of ethyl α-phen-

acetylacetoacetate gave ethyl α-bromo-α-phenacetylacetoacetate (III). Similarly, bromination of an acetic acid solution of ω,ω-diphenacetylacetophenone produced the 3-bromo compound (IV).

On bromination of phenacetylacetophenone in ether an $\alpha \rightarrow \gamma$ migration occurred to give 4-bromophenacetylacetophenone (V). Migration also occurred when ethyl benzoylacetoacetate was brominated: the γ-bromo compound was produced (VI).

$$\begin{matrix} CH_3CO \diagdown & \\ & CHCOOEt \\ CH_3CO \diagup & \end{matrix} \xrightarrow{Br_2} \begin{matrix} BrCH_2CO \diagdown & \\ & CHCOOEt \\ BrCH_2CO \diagup & \end{matrix}$$

I II

$$\begin{matrix} CH_3CO \diagdown & Br \\ & C\text{-}COOEt \\ C_6H_5CH_2CO \diagup & \end{matrix} \qquad \begin{matrix} C_6H_5CH_2CO \diagdown & Br \\ & C\text{-}COC_6H_5 \\ C_6H_5CH_2CO \diagup & \end{matrix}$$

III IV

$$\begin{matrix} Br \\ C_6H_5CHCOCH_2COC_6H_5 \end{matrix} \qquad \begin{matrix} BrCH_2CO \diagdown & \\ & CHCOOEt \\ C_6H_5CO \diagup & \end{matrix}$$

V VI

Mechanism: Kharasch (8) has demonstrated that ethyl acetoacetate yields more than 80% of the α-bromo compound in the absence of air, light, or peroxides. When bromination occurs in the presence of one of these three factors, 90% of the γ-bromo compound is produced. In a manner analogous to the effect of peroxides in the addition of hydrogen bromide to unsaturated compounds, it appears to Kharasch that the rearrangement is caused by free radical chain reactions involving bromine atoms.

Kröhnke (4) has proposed an ionic theory of bromine substitution based upon the great ease of removal by reduction of the positive α-bromine in α-bromo-1,3-diketones and β-ketoesters. These α-bromodicarbonyl compounds which undergo the rearrangement manifest their ease of reduction by the complete and rapid liberation of iodine from an alcohol or acetone solution of potassium iodide. This theory assumes that the bromine atom first substitutes on the α-carbon atom of the enol form of the β-ketoester or 1,3-diketone in a reversible manner. Due to the powerful electropositivity of the two adjacent carbonyl groups, the bromine atom becomes electropositive and is reduced from the α-position by the hydrogen bromide formed during the substitution reaction. The bromine, meanwhile, slowly substitutes in the γ-position irreversibly.

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ADDITION PRODUCTS OF AMINES AND ACETYLENE

Reported by William D. Emmons — October 14, 1949

Introduction.--In the older literature there are a number of reports of condensations between aromatic amines and acetylene. Among the catalysts employed have been nickel (1) and the salts of mercury, copper, and silver (2). Aromatic amines have also been added to monosubstituted acetylenes in the presence of boron trifluoride and mercuric oxide (3). Recently, however, a different type of reaction has been described between acetylene and either primary or secondary amines in the presence of a copper acetylide catalyst (4,5).

Synthesis of Aminobutynes.--Acetylene partially diluted with nitrogen and under a pressure of from 150 to 200 lbs./in.^{2} was introduced into an autoclave containing diethyl amine and cuprous chloride. The product isolated after completion of the reaction was 3-diethyl aminobutyne-1 (I) in 65% yield. Two molecules of acetylene thus reacted with one of the amine. The intermediate in the reaction is presumably the vinyl amine (II), since vinyl acetylene (III) reacts with amines under the conditions employed to give 2-aminobutadienes. The structure of the product (I) was established by

$(C_2H_5)_2NCH(CH_3)C{\equiv}CH$ — I

$(C_2H_5)_2NCH{=}CH_2$ — II

$CH_2{=}CHC{\equiv}CH$ — III

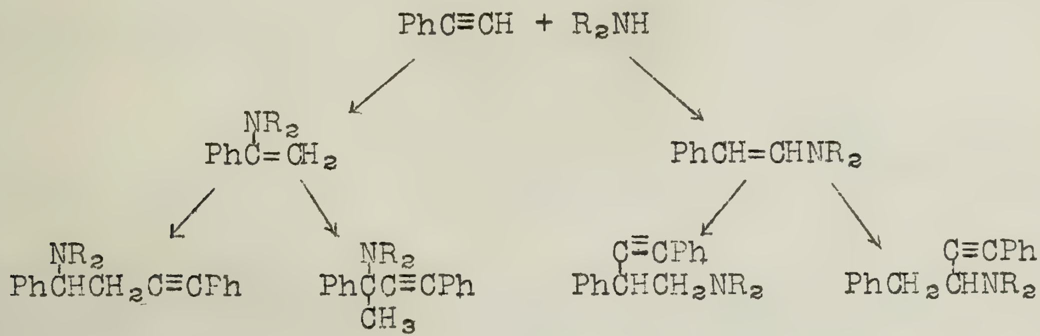
comparison with an authentic specimen of the aminobutyne obtained by another route (6) as well as by catalytic hydrogenation to the saturated amine. The reaction was also carried out with dimethyl amine and morpholine. The corresponding butynes were obtained in yields of 63% and 80% respectively. In these last two cases tetrahydrofuran was employed as the solvent.

The reaction of primary amines is somewhat more complicated. The formation of higher condensation products with isopropyl amine was particularly great. However, good yields of the expected aminobutynes were obtained from n-butyl (65%), cyclohexyl (70%), and benzyl amines (70%). Hexamethylene diamine reacted to give a product (IV) formed by reaction of only one of the amino groups in 40% yield. Aniline could be added to acetylene but only under somewhat different conditions. The aniline in alcoholic solution was converted partly to the acetate and then treated with acetylene in the presence of preformed copper acetylide on filter-cel catalyst. A 25% yield of 3-anilinobutyne-1 (V) was thus obtained.

$NH_2(CH_2)_6NHCH(CH_3)C{\equiv}CH$ — IV

$PhNHCH(CH_3)C{\equiv}CH$ — V

The reaction of phenyl acetylene and amines was also studied (7). It was hoped that phenyl acetylene could be used as a laboratory model for the reactions of acetylene itself, since the latter is not only difficult to handle but is very sensitive to surface conditions within the reaction vessel. According to the previously proposed scheme four possible products could be obtained. The reaction was carried out, and two isomeric bases were isolated. One was identified as (IX) by synthesis, and indirect evidence showed that the other was (VI). The secondary amine used in this case was morpholine.



VI VII VIII IX

Addition of Acetylene to Tertiary Amines.--Acetylene under pressure and aqueous trimethyl amine react to give trimethylvinyl ammonium hydroxide (8). This appears to be an attractive synthesis for a powerful organic base which should have commercial applications. In addition to trimethylvinyl ammonium hydroxide or neurin, as it is sometimes called, appreciable amounts of tetramethyl ammonium hydroxide are produced. At temperatures below 50°C. neurin is the chief product, while above 100°C. tetramethyl ammonium hydroxide is practically the only product. The spontaneous conversion of neurin to tetramethyl ammonium hydroxide may be demonstrated by heating the former above 100°C. The mechanism is not clear but trimethyl amine is first evolved, and this is probably followed by some sort of transmethylation, as indicated below. Dimethylvinyl amine is known to be unstable and rapidly polymerizes.

$$CH_2{=}CHN(CH_3)_3OH \rightarrow (CH_3)_3N + CH_3CHO$$

$$(CH_3)_3N + CH_2{=}CHN(CH_3)_3OH \rightarrow (CH_3)_4NOH + [(CH_3)_2NCH{=}CH_2]$$

Reactions of Aminobutynes.--The aminobutynes are reactive compounds and offer numerous possibilities as synthetic intermediates. Among the more useful reactions that may be carried out with them are hydration, Mannich reactions, and oxidation (9). The hydration of 3-dialkyl aminobutynes-1 with mineral acids in the presence of mercury salts gives the corresponding amino ketones. Mercuric

sulfate and sulfuric acid are generally employed for the reaction.

$$(C_2H_5)_2N\overset{CH_3}{C}HC\equiv CH \xrightarrow{H_2O} (C_2H_5)_2N\overset{CH_3}{C}HCOCH_3$$

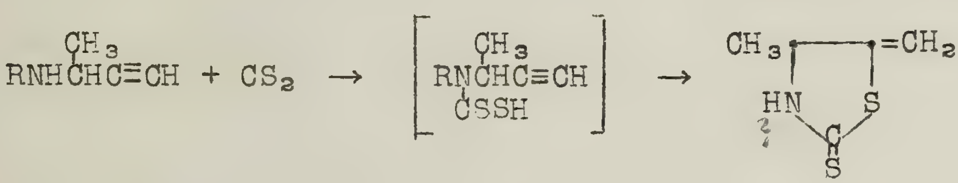
In common with other monosubstituted acetylenes, aminobutynes react readily in the Mannich reaction. Thus 3-diethyl aminobutyne-1 reacted with paraformaldehyde and diethylamine or piperidine to give the acetylenic diamines in yields of 70% and 55% respectively. Catalytic hydrogenation with Raney nickel gave the corresponding 1,4 diamino pentanes.

$$(C_2H_5)_2N\overset{CH_3}{C}HC\equiv CH + CH_2O + R_2NH \rightarrow (C_2H_5)_2N\overset{CH_3}{C}HC\equiv CCH_2NR_2$$

The air oxidation of acetylenes in the presence of cuprous salts to give diacetylenes has previously been reported with acetylenic hydrocarbons (10). In application of the reaction to aminobutynes, oxidation was carried out by bubbling air through an aqueous solution of the amine hydrochloride in the presence of only a catalytic amount of cuprous chloride. In this manner the diacetylenic diamines were prepared in yields of 66%-95%.

$$2\ R_2N\overset{CH_3}{C}HC\equiv CH \rightarrow R_2N\overset{CH_3}{C}HC\equiv C-C\equiv C\overset{CH_3}{C}HNR_2$$

Monoalkyl aminobutynes will also add to carbon disulfide effecting a rather interesting ring closure (11). The reaction occurs in the presence of sodium hydroxide, and the product obtained has been assigned the thiazolidine ring on the basis of available evidence. The yields are excellent and vary from 58% to 87%.



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METHYL SUBSTITUTED LONG CHAIN ACIDS

Reported by K. A. Schowalter October 14, 1949

Branched chain fatty acids occur in nature in bile acids and in certain acid-fast bacteria. In investigating the lipid or fat fraction of tubercle bacilli, Anderson and his co-workers isolated a group of liquid fatty acids (1). One of these, tuberculostearic ($C_{19}H_{38}O_2$) has been identified as 10 methyl stearic acid (2). Another, phthioic acid ($C_{26}H_{52}O_2$), is of particular interest because the purified acid when injected into animals produces lesions similar to those of tuberculosis. The structure of phthioic acid is unknown. Based upon degradation experiments, the molecule was believed to be a long chain of 22 carbons with the remaining 4 carbons distributed laterally as substituted methyl groups (3,4,5, This interest in the structure of phthioic acid has stimulated research in the synthesis of methyl substituted acids. Many of these acids have been prepared and some of them tested biologically and found to possess the ability to cause the tuberculosis-like lesions caused by the natural acid (7,8).

A survey of the literature yielded the synthesis procedures for the mono-, di-, and tri-methyl acids listed below.

Mono Methyl

$C_3-\underset{C}{C}-C_5-COOH$ (6)

$C_4-\underset{C}{C}-C_4-COOH$ I (6)

$C_5-\underset{C}{C}-C_3-COOH$ VI (6)

$C_6-\underset{C}{C}-C_2-COOH$ V (6)

$C_7-\underset{C}{C}-C-COOH$ IV (6)

$C-\underset{C}{C}-C_{12}-COOH$ (16)

$C-\underset{C}{C}-C_{15}-COOH$ (9)

$C_2-\underset{C}{C}-C_{14}-COOH$ (10)

$C_3-\underset{C}{C}-C_{13}-COOH$ (11)

$C_8-\underset{C}{C}-C_8-COOH$ (2,17)

Di Methyl

$C_6-\underset{C}{C}-C_2-\underset{C}{C}-C_{11}-COOH$ (7)

$C_6-\underset{C}{C}-C_3-\underset{C}{C}-C_{11}-COOH$ (7)

$C_7-\underset{C}{C}-C_2-\underset{C}{C}-C_{11}-COOH$ (6)

$C_{10}-\underset{C}{C}-C_8-\underset{C}{C}-C-COOH$ (7)

$C_7-\underset{C}{C}-C_2-\underset{C}{C}-C_{12}-COOH$ (6)

$C_{12}-\underset{C}{C}-C_{10}-\underset{C}{C}-COOH$ (6)

Tri Methyl

$C_6-\underset{C}{C}-C_2-\underset{C}{C}-C_9-\underset{C}{C}-C-COOH$ (8)

$C_7-\underset{C}{C}-C_2-\underset{C}{C}-C_8-\underset{C}{C}-C-COOH$ (8)

$C_7-\underset{C}{C}-C_2-\underset{C}{C}-C_9-\underset{C}{C}-COOH$ III (8)

$C_{12}-\underset{\substack{| \\ C}}{C}-C_4-COOH$ (15)

$C_{16}-\underset{\substack{| \\ C}}{C}-COOH$ (15)

$C_{20}-\underset{\substack{| \\ C}}{C}-C-COOH$ (7)

$C_{10}-\underset{\substack{| \\ C}}{C}-C_{12}-COOH$ (11)

$C_{14}-\underset{\substack{| \\ C}}{C}-C_8-COOH$ (10)

$C_{18}-\underset{\substack{| \\ C}}{C}-C_4-COOH$ (10)

$C_4-\underset{\substack{| \\ C}}{C}-C_5-\underset{\substack{| \\ C}}{C}-C_9-\underset{\substack{| \\ C}}{C}-C-COOH$ II (6)

$C_7-\underset{\substack{| \\ C}}{C}-C_2-\underset{\substack{| \\ C}}{C}-C_8-\underset{\substack{| \\ C}}{C}-C_2-COOH$ (3)

Roman numerals refer to the chart on page 4. Numbers in parentheses are references.

The procedures for the most part consisted of a series of the more common, simple reactions of organic chemistry. The reactions employed may be classified as follows:

A. Reactions for lengthening the chain.

1. Grignard reaction or a series of Grignard reactions.
2. Malonic ester reaction with a primary halogen atom followed by hydrolysis and decarboxylation.
3. Reaction of NaCN with a primary halide followed by hydrolysis.
4. Acetoacetic ester reaction (6,17).
5. Alkyl cadmium reaction with an acid chloride followed by a Clemmensen reduction of the carbonyl group (9,10, 11,12).
6. Condensation of an acid chloride with a primary iodide through the organozinc compound (2,7,8).
7. Arndt-Eistert reaction (6).

B. Reactions for introducing the side chain methyl groups in addition to lengthening the chain.

1. Conversion of acid chloride to a methyl ketone by means of $(CH_3)_2Cd$ or CH_3ZnI and reaction of the ketone with RMgX (6,8,10).
2. Condensation of cyanoacetic ester with a methyl ketone in the presence of ammonium acetate and acetic acid to give a product of the type $R-\underset{\substack{| \\ C}}{C}=\underset{\substack{| \\ CN}}{C}-COOEt$ which is then hydrogenated, hydrolyzed and decarboxylated.
3. Conversion of a $-C\equiv N$ group to a methyl ketone by means of CH_3MgI and further reaction of the ketone with RMgX (6).
4. Reaction of diethyl methyl malonate with a primary halogen atom (6,15).

5. Reaction of malonic ester with a secondary halogen atom.
6. Reaction of an alkyl Grignard with acetaldehyde (6).
7. The reaction of ethyl levulinate with a Grignard to yield a substituted γ-lactone. The γ-lactone may then be hydrogenated with copper chromite to the 4 methyl alcohol (14) or converted to the 4 methyl acid by treatment with $SOCl_2$, EtOH and HCl followed by dehydration, hydrogenation, and hydrolysis (11).

The above list includes the more important steps of the various syntheses, references are given in those cases which are sufficiently specific. The syntheses for six of the acids have been diagrammed on page 4 to serve as general examples.

In general the starting materials were C_{10} or less straight chain compounds which were built up with step by step purification. Use of commercial secondary halides and substituted methyl (iso) compounds was avoided due to the possibility of isomeric impurities. Considerable use was made of selective Grignard reactions in which a calculated amount of the Grignard reagent was added to a known amount of a keto ester to yield the hydroxy-ester. Cason and his co-workers made extensive use of organo-cadmium compounds on ω carboethoxy acid chlorides.

The synthesis of these methyl substituted acids has done much to facilitate further investigation of the structure of phthioic acid and may eventually form the basis of the proof of its structure.

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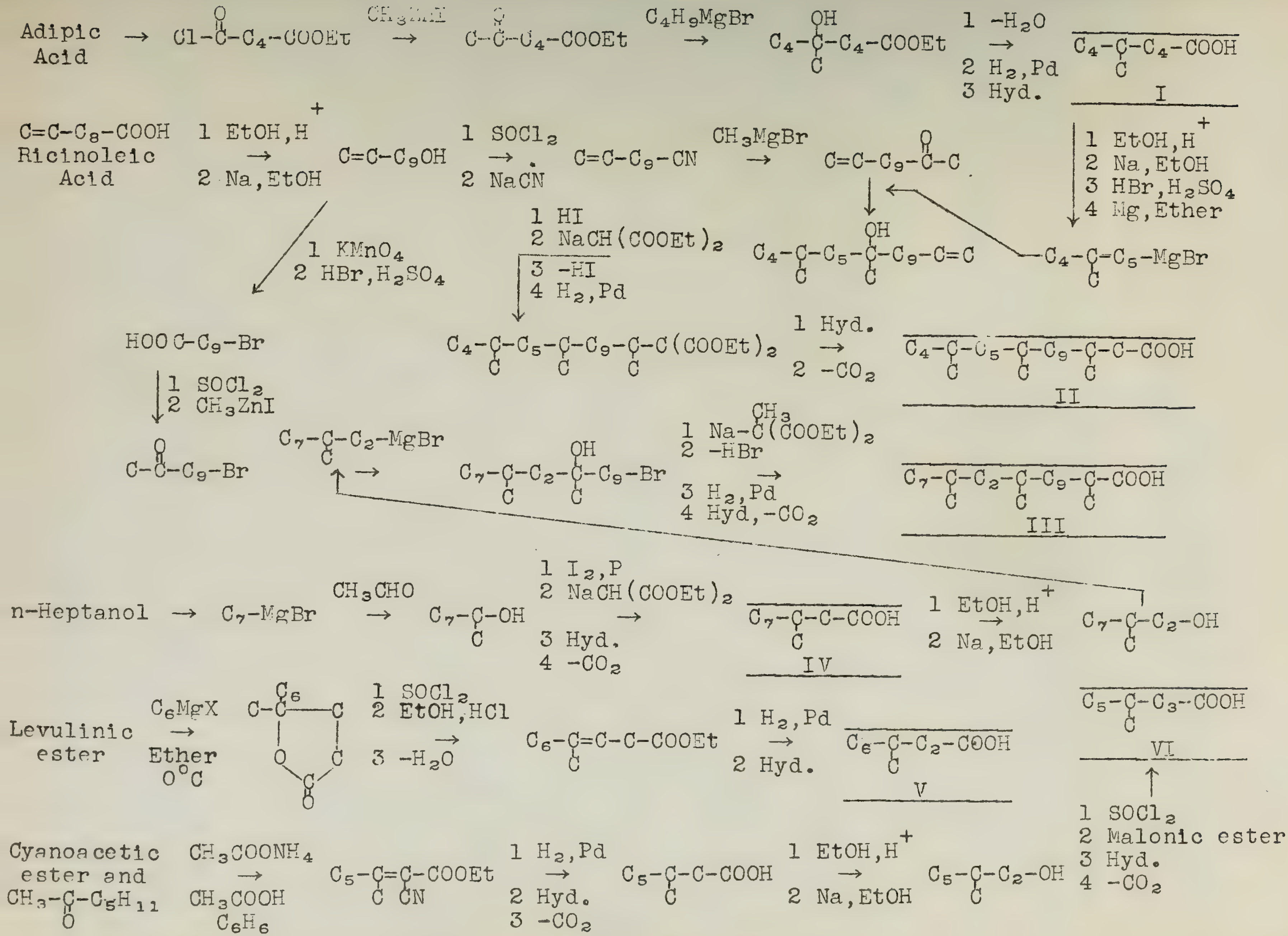

Adipic Acid
Ricinoleic Acid
n-Heptanol
Levulinic ester
Cyanoacetic ester and
I
II
III
IV
V
VI

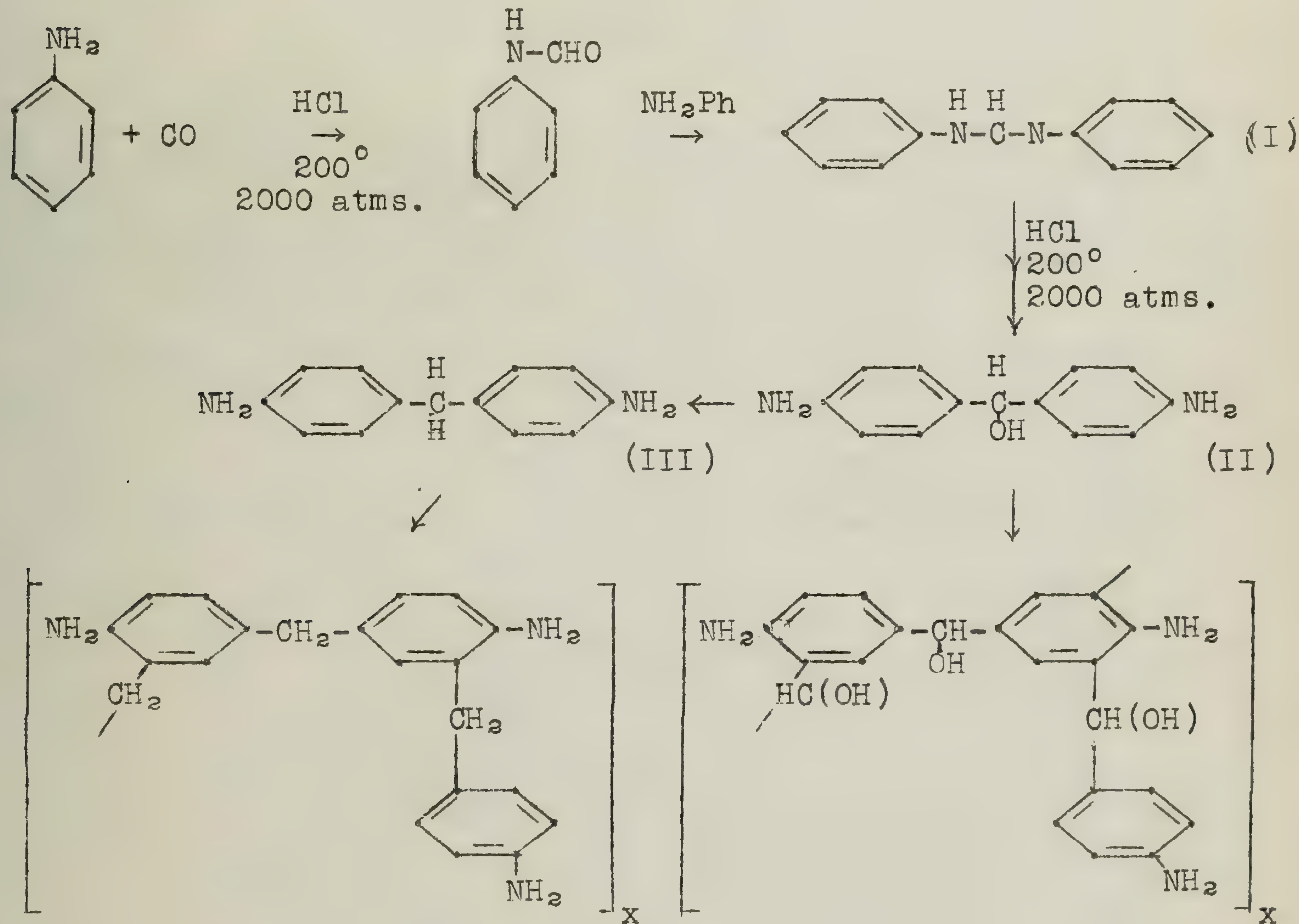
SOME HIGH PRESSURE REACTIONS OF CARBON MONOXIDE

Reported by Sheldon S. Simon   October 14, 1949

The use of carbon monoxide in high pressure reactions has been discussed before (1,2) but recently a new series of reactions were developed which combine carbon monoxide and aryl amines, hydrazine and also employs it as a reducing agent for certain organic compounds.

It has been observed that carbon monoxide reacts with certain aryl amines in the presence of an acid catalyst at high temperature and pressure to give a basic product of high molecular weight.

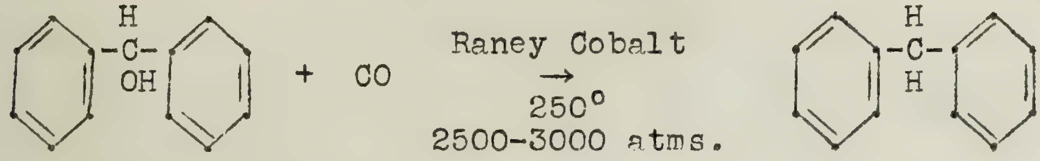
The observation was not pursued until recently when the reaction was applied to aniline (3).



The course of the reaction was postulated to involve the interaction of aniline and carbon monoxide to give formanilide which then reacted with more aniline to form the unstable intermediate (I) which undergoes rearrangement in the acid medium to pp'-diaminodiphenyl carbinol (II). The carbinol is then reduced by the carbon monoxide to pp'-diaminodiphenylmethane (III). Compounds (II) and (III) contain unsubstituted positions ortho to the amino group and therefore can probably react further with more carbon monoxide to give the polymeric products (IV) and (V).

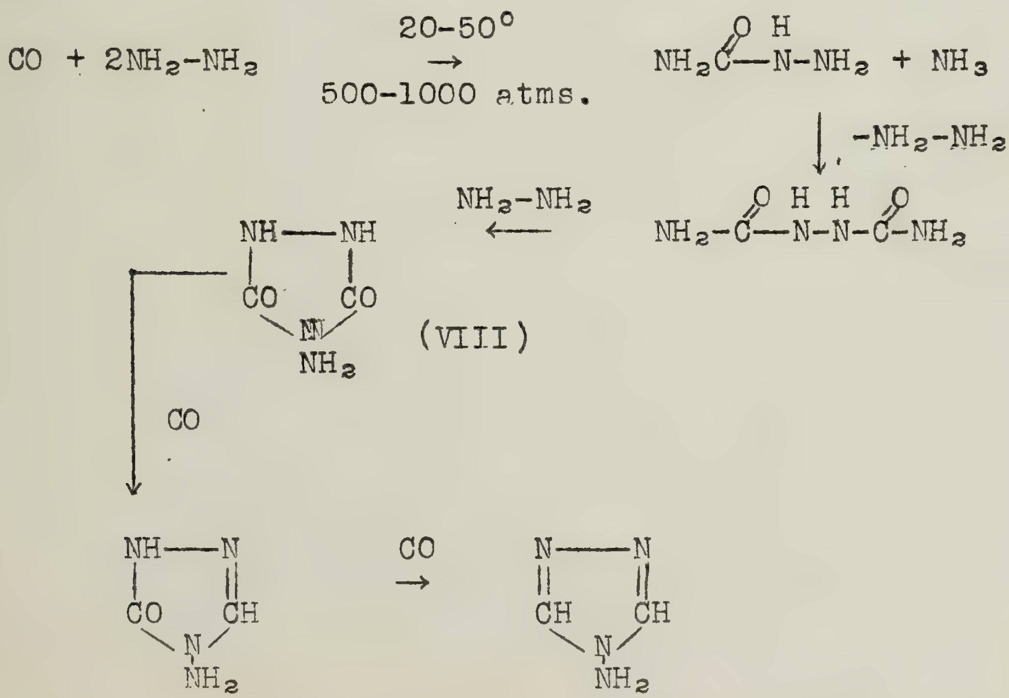
It has been shown (3) that diaryl carbinols and many other organic compounds will undergo transformations in the presence of carbon monoxide, under anhydrous conditions and in the absence of a catalyst, at high temperatures and pressures. Nitro, nitroso and azoxybenzenes are reduced to azobenzene; N-phenylbenzaldoxime is reduced to benzylideneaniline. Aryl carbinols form ethers under these conditions.

In the presence of Raney Cobalt, aryl alcohols undergo reduction.



Benzaldehyde afforded a surprising result in the presence of the catalyst. When it was placed in an atmosphere of carbon monoxide at 250° and 3000 atms. a mixture of toluene and benzoic acid was formed. It was postulated that the catalyst induced a Cannizzaro reaction to give benzoic acid and benzyl alcohol, which was then reduced by the carbon monoxide.

A high pressure reaction of carbon monoxide and hydrazine produces triazolones (VI) or triazoles (VII) (3).



(VI) (VII)

The structure of these compounds, (VI) and (VII) (4), were established by conducting the reaction under milder conditions.

By analogy to the interaction of carbon monoxide and ammonia one would expect the formation of a formyl hydrazide which tends to form cyclic compounds. However in this reaction the hydrazine is reduced to semicarbazide and ammonia. The former loses hydrazine to form compound (VIII) which, in the presence of excess hydrazine, forms compounds (VI) and (VII).

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THE SYNTHESIS AND REACTIONS OF α,β-DIACETYLETHYLENE

Reported by Charles H. Benton October 21, 1949

α,β-Diacetylethylene was first prepared by Armstrong and Robinson (1) in 1934. These workers oxidized acetonylacetone with selenous acid and obtained a 15% yield.

(I) $$CH_3-\overset{O}{\overset{\|}{C}}-CH_2\cdot CH_2-\overset{O}{\overset{\|}{C}}-CH_3 \xrightarrow[SeO_2]{[O]} CH_3-\overset{O}{\overset{\|}{C}}-CH{=}CH-\overset{O}{\overset{\|}{C}}-CH_3$$

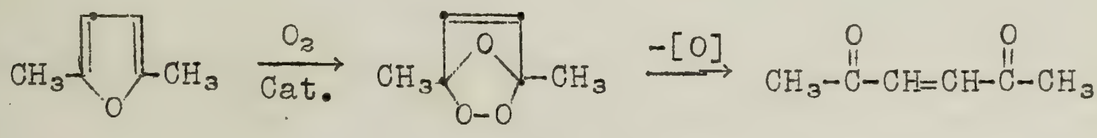
Grundmann (2) found that diacetylethylene could be prepared in 20% yield by the catalytic decomposition of diazoacetone over a copper oxide catalyst in an inert solvent.

(II) $$CH_3-\overset{O}{\overset{\|}{C}}-CHN_2 \xrightarrow[CuO]{\Delta} CH_3-\overset{O}{\overset{\|}{C}}-CH{=}CH-\overset{O}{\overset{\|}{C}}-CH_3$$

The method of the English workers was improved by Goldberg and Müller (3) in 1938 to give a 21% yield. Diels and Olsen (4) thought they had discovered a new synthesis from 2,5-dimethylfuran, acetylene and water. However, in 1944, Schenck (5) found that 2,5-dimethylfuran was oxidized spontaneously in the air to give yields of diacetylethylene that approached 50%. He showed that the failure of Diels and Olsen completely to exclude air was responsible for the presence of the product in the reaction mixture and that there was no basis for the use of their reagents.

The equation that Schenck postulates (III) involves the intermediate formation of the ozonide (6).

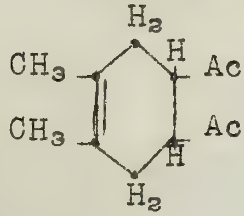
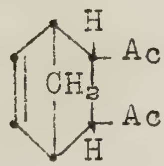
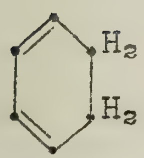
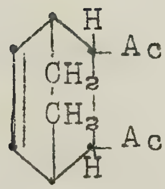
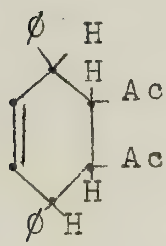
(III)



Although Grundmann claimed that he obtained diacetylethylene in a completely colorless form, m.p. 78° C., all other workers have reported a light yellow compound with the same melting point. On the basis of this coloration, Armstrong and Robinson postulated the trans configuration for the compound by

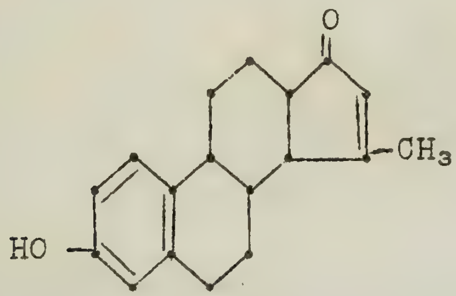
analogy to α,β-dibenzoylethylene, of which the cis form is colorless and the trans, yellow. No one has been able to isolate the second isomer or to transform one isomer into the other.

Diacylethylenes, in general, are most useful synthetically as dienophiles, although dibenzoylethylene reacts with hydrazine to form 3,6-diphenylpyridazine (7). This same reaction with the diacetyl compound yields only polymeric products. The following compounds have been made through the diene synthesis from the compounds indicated and diacetylethylene:

From	Compound	Reference
$CH_2=C(CH_3)-C(CH_3)=CH_2$		3
		5
		5
ø-CH=CH-CH=CH-ø		5

Goldberg and Müller have used diacetylethylene in an interesting synthesis of compounds related to the female sex hormones. Starting from 6-methoxytetralone, they proceeded through acetylene magnesium bromide, dehydration and

the addition of one mole of hydrogen to 1-vinyl-6-methoxy-3,4-dihydronaphthalene. This compound was treated with diacetylethylene in the diene synthesis. The product was treated with one mole equivalent of hydrogen and the ring closed with sodium methoxide in methanol to give the methyl ether of 15-methyl-15-dehydro-x-norestrone. This compound was treated with HBr in HOAc to give the phenolic substance (or its isomer):



This compound was found to have estrogenic activity with rats and from this fact it is postulated that rings C and D are of the trans configuration in analogy to the proposed structure for the natural hormone.

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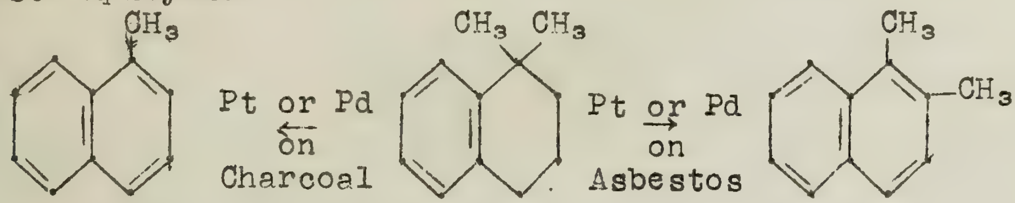
MIGRATION AND ELIMINATION OF ALKYL GROUPS IN THE CATALYTIC DEHYDROGENATION OF HYDROAROMATIC COMPOUNDS

Reported by H. N. Cripps   October 21, 1949

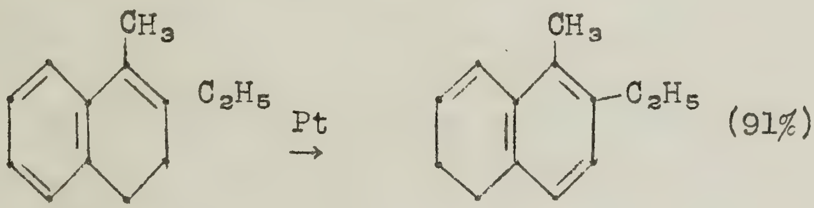
Linstead (1,2) observed that methyl groups attached to a quaternary carbon atom either migrated or were eliminated in the catalytic dehydrogenation of hydroaromatic compounds in the liquid or vapor phase. Migration or elimination was determined by the catalyst carrier and not by the metal catalyst employed.



Methyl groups not attached to a quaternary carbon atom remained intact throughout the dehydrogenation.

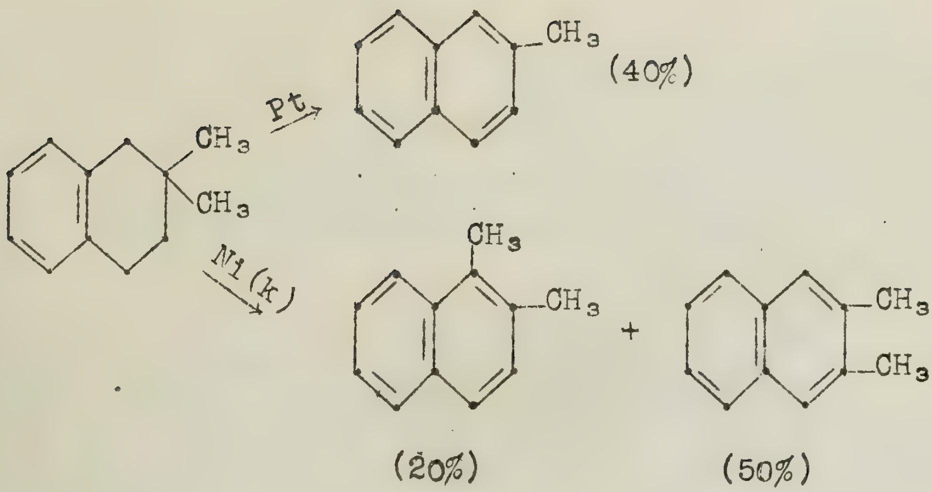
Recently Adkins and his co-workers (3-7) have studied these phenomena further. Three catalysts were employed: platinum on charcoal, nickel on nickel chromite and nickel on kieselguhr. A large number of hydroaromatic compounds having the napthalene, phenanthrene and anthracene nuclei were synthesized and subjected to catalytic dehydrogenation with benzene as an hydrogen acceptor.

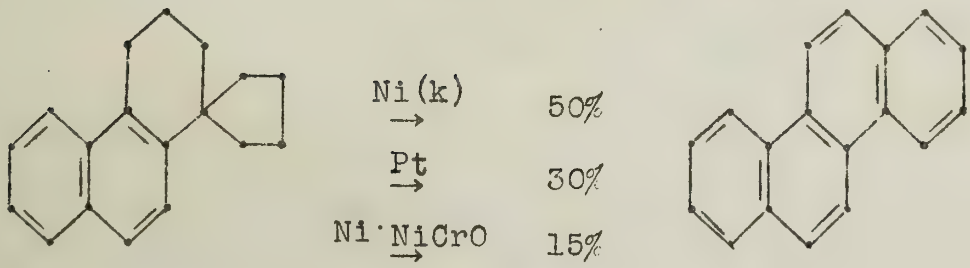
The following generalizations can be made: (1) alkyl groups which are not attached to a quaternary carbon atom are unaffected in the dehydrogenation process.



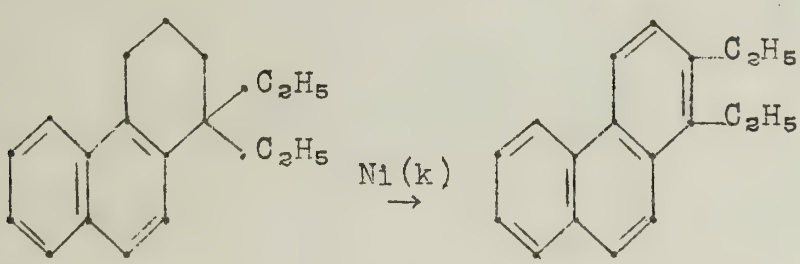
(2) For a dehydrogenation which does not involve a migration, the platinum catalyst gives the best yields.

(3) The platinum catalyst induces aromatization by the elimination of an alkyl group, whereas the nickel on kieselguhr catalyst favors the migration of an alkyl group. The nickel on nickel chromite catalyst tends to induce both changes.

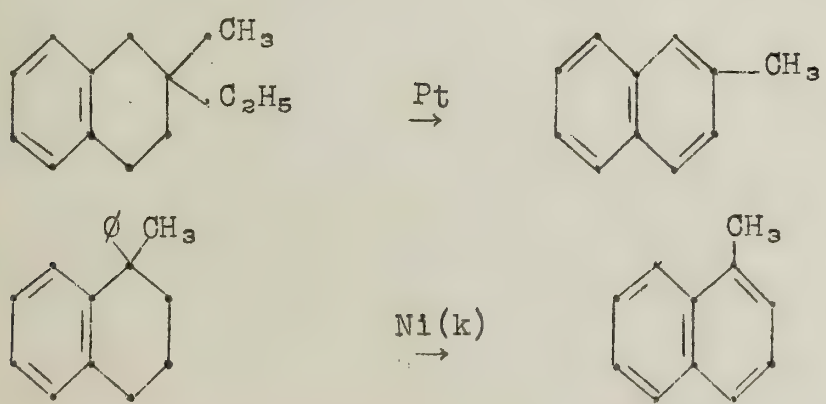




(4) Alkyl groups other than methyl may migrate.

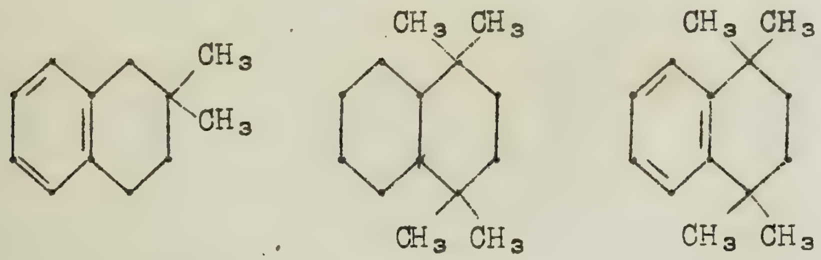


(5) When elimination occurs, the largest alkyl group is eliminated.



(6) An alkyl group may migrate to more than one position thus giving rise to isomeric products. (See example in (3)).

(7) Aromatization resulting from the cleavage of a carbon-carbon bond, requires more drastic conditions than are required for a simple elimination of hydrogen. Hence tetralin aromatizes more readily than I. II is converted to III in 90% yield without the formation of appreciable amounts of methyl naphthalenes. The 1,1,4,4 tetraalkyl tetralins are not dehydrogenated to any appreciable extent under the conditions employed.



I II III

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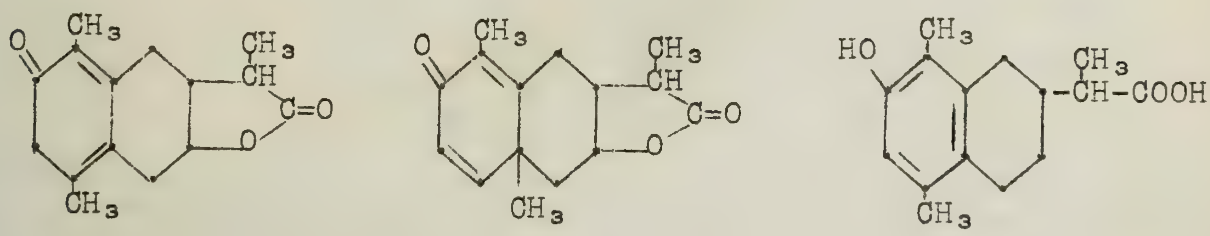
CHEMISTRY OF THE SANTONINS

Reported by Charles N. Winnick October 21, 1949

Santonin is obtained from the plants of the genus Artemisia. It comprises from 2-3 1/2% of the flower heads of Artemisia maritima (1). It is widely used as an antihelmintic.

The investigations of a large number of Italian chemists culminated in the proposal of structure (I) in 1892, which was based on degradation studies (2).

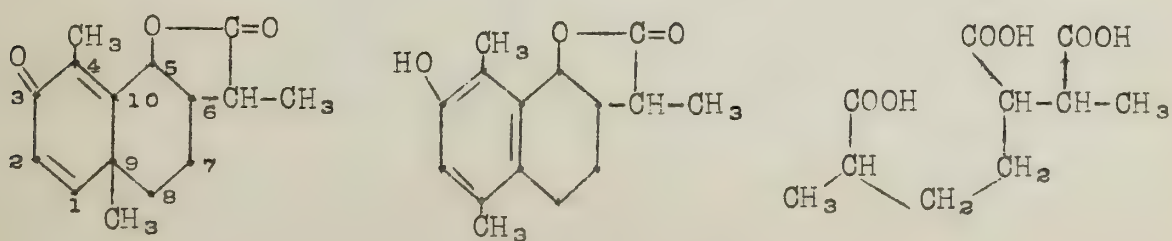


I II III

In 1929, Clemo et al. (1) proposed another structure (II). The revision of the older structure was based on the failure of santonin to give a piperoylidene derivative, indicating the absence of an α-methylene group. Treatment of santonin with acids has long been known to produce a desmotroposantonin in which the methyl groups were para. Its formation, therefore, must include a shift of a methyl group, which has been demonstrated in other cases.

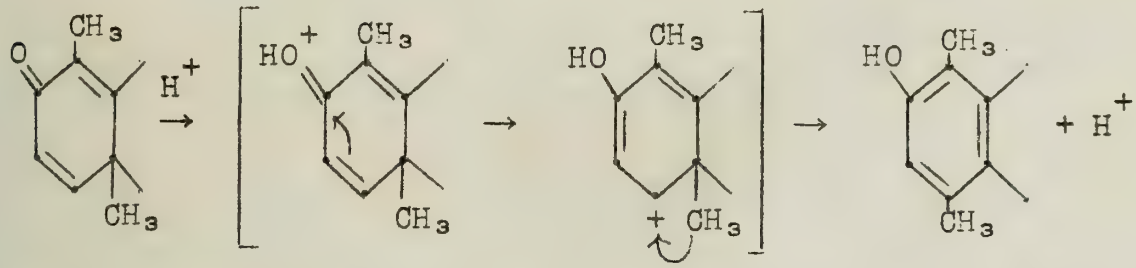
Reduction of santonin produces <u>dl</u>-santonous acid (III) which was synthesized and proven identical with the natural product. Reduction of santonin to the tetrahydro compound, followed by reduction of the keto group with zinc and hydrochloric acid gave a product which yielded 1-methyl 7-ethyl naphthalene upon selenium dehydrogenation (3). This work, verified by Ruzicka independently (4), indicates the angular position of the methyl group.

Clemo modified his structure of santonin slightly to (IV) later (5), and was able to synthesize the corresponding desmotroposantonin (V) which was shown to be identical with natural material.



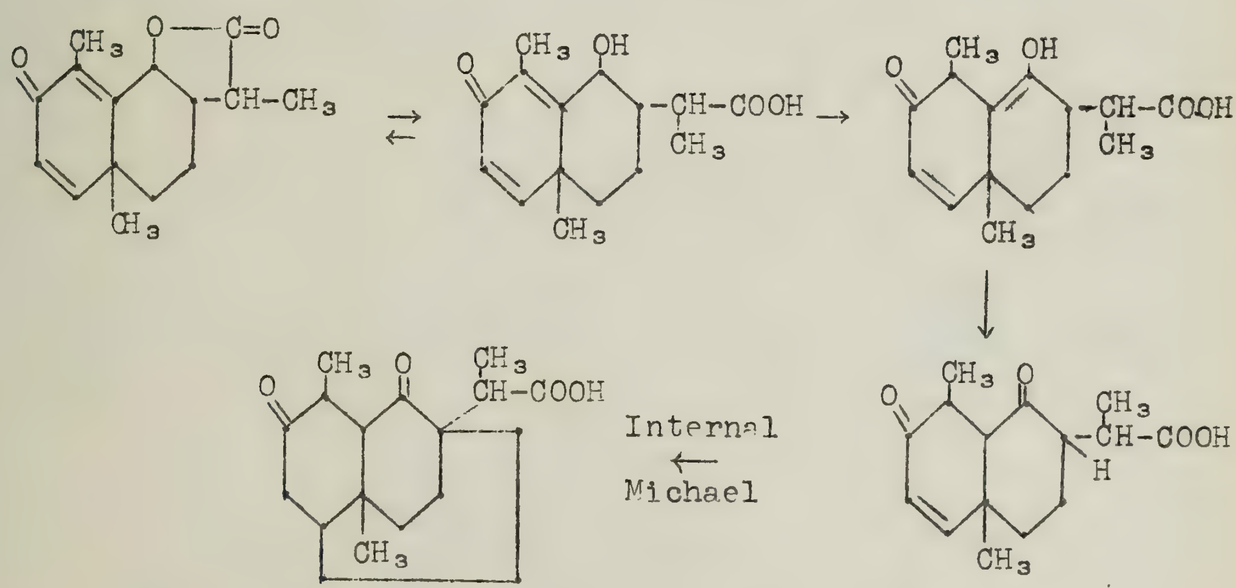
IV V VI

Ruzicka was also able to synthesize the tricarboxylic acid (VI) derived from santonin by permanganate oxidation, giving additional proof of the structure (6). Huang-Minlon has proposed the following mechanism for the conversion of santonin to desmotroposantonin (7).



The first claim for a synthesis of santonin was made in 1943 (8). However, Clemo and his group could not duplicate the synthesis (9). The latest synthesis was reported in 1948 from cyclohexanone and β-bromo propionic ester (10).

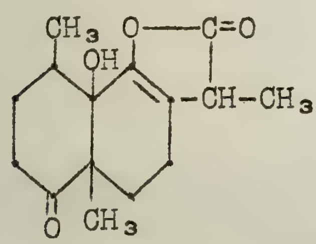
Treatment of santonin with aqueous alkali produces santonic acid. The structure of this acid has been in doubt until recently. Wedekind reinvestigated santonic acid in 1934 (11) and discovered many of its functional groups. In a recent paper (12) Woodward et al. have analyzed the known information and postulated a structure, which is formed by the following series of steps.



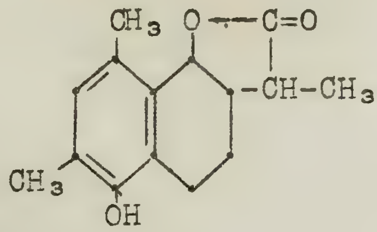
Santonic Acid

Santonic acid can be degraded to a 2,3,6, tricarboxy heptane (santoronic acid) identical with a synthetic product and which is a stereoisomer of the acid V.

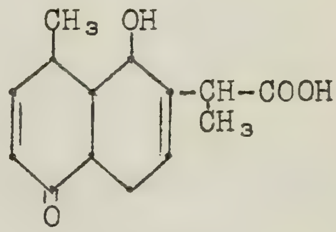
<u>Pseudosantonin</u>: Cocker and Clemo have isolated from the Artemisia species another compound which they have called pseudosantonin (13). It has the empirical formula $C_{15}H_{20}O_4$ and can be converted to a desmotropopseudosantonin by 55% sulfuric acid. On fusion with potassium hydroxide, 2,4-dimethylnaphthol is formed. Selenium dehydrogenation yields 1-methyl 7-ethyl naphthalene. It contains a ketonic carbonyl, a tertiary hydroxyl, and an unsaturated lactone grouping. The desmotropopseudosantonin gave no ketone derivatives and could not be oxidized. The proposed structure (VII) is quite similar to santonin (14).



VII



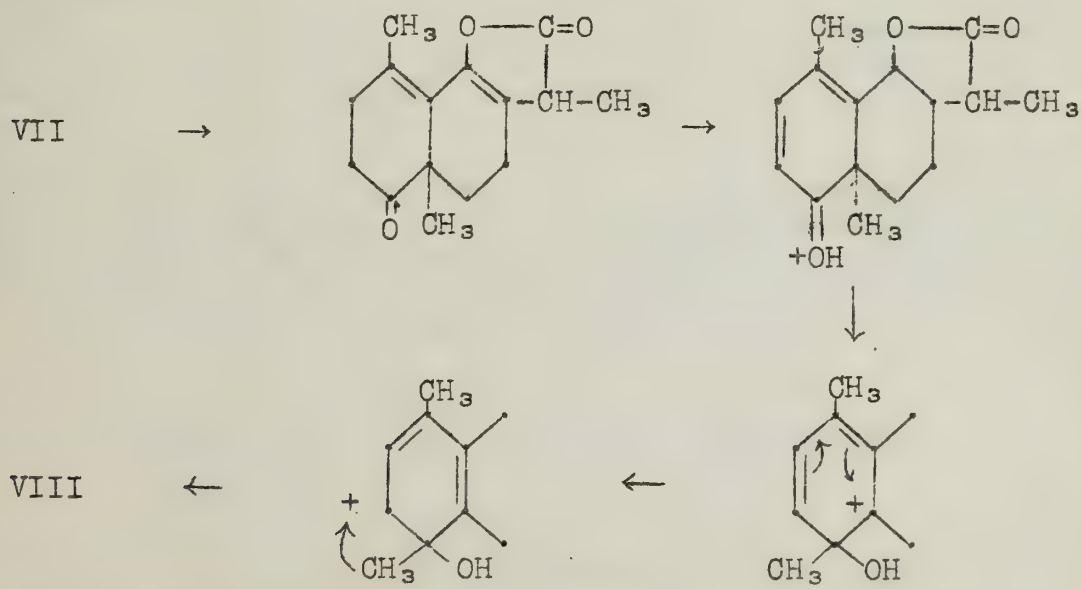
VIII



IX

The α-β unsaturated lactone and the other β-γ isomer are also possibilities.

Conversion of pseudosantonin to the desmotropo form (VIII) would involve the shift of a methyl group over two carbons if structure (VII) is accepted, for which transformation, Cocker has proposed a mechanism (15).



The dl methyl ether of the compound having structure VIII was synthesized but all attempts to racemize the natural product failed, and no comparison could be made (14).

After intensive investigation of the butenolide system (16) in which he compared pseudosantonin with other unsaturated lactones, Cocker concluded that VI best represents pseudosantonin. He has also noted the isolation of an intermediate in the conversion of pseudosantonin to the desmotropo form, to which he has assigned structure (IX). In addition, he has isolated three other dextro desmotropo pseudosantonins (17).

Ψ Santonin

$\downarrow H_2SO_4$

+ β desmotropo Ψ santonin $\qquad$ + α isodesmotropo Ψ santonin

$\downarrow$ NaOH $\qquad$ $\downarrow K_2CO_3$

+ α desmotropo Ψ santonin $\qquad$ + β isodesmotropo Ψ santonin

Stereochemistry: The first stereoisomer of santonin was reported by Clemo (17) and designated β-santonin. It differed only in melting point and rotation from santonin itself. Clemo demonstrated the following interconversions.

β santonin $\xrightarrow{H_2SO_4}$ l-desmotropo β santonin $\searrow$ d-santanous acid

$\downarrow$ KOH

santonin $\xrightarrow{H_2SO_4}$ l-desmotropo santonin $\nearrow$ d-santanous acid

Huang-Minlon reported in 1943 two new desmotropo santonins (18). In order to eliminate confusion he introduced a new nomenclature using α and β to designate low melting and high melting forms respectively. He was able to establish a unioue cycle involving four stereoisomeric desmotroposantonins.

d-β-desmotroposantonin $\xrightarrow{OH^-}$ d-α-desmotroposantonin

$\uparrow H^+$ $\qquad$ $\downarrow H^+$

l-α-desmotroposantonin $\xleftarrow{OH^-}$ l-β-desmotroposantonin

dl-α-desmotroposantonin $\rightleftarrows$ dl-β-desmotroposantonin

The bromo derivatives of desmotroposantonin undergo similar transformations (19) while the nitro derivatives do not (20). He considers the acid treatment to invert the configurations at C5 and C6, and the basic treatment to invert C11 (7).

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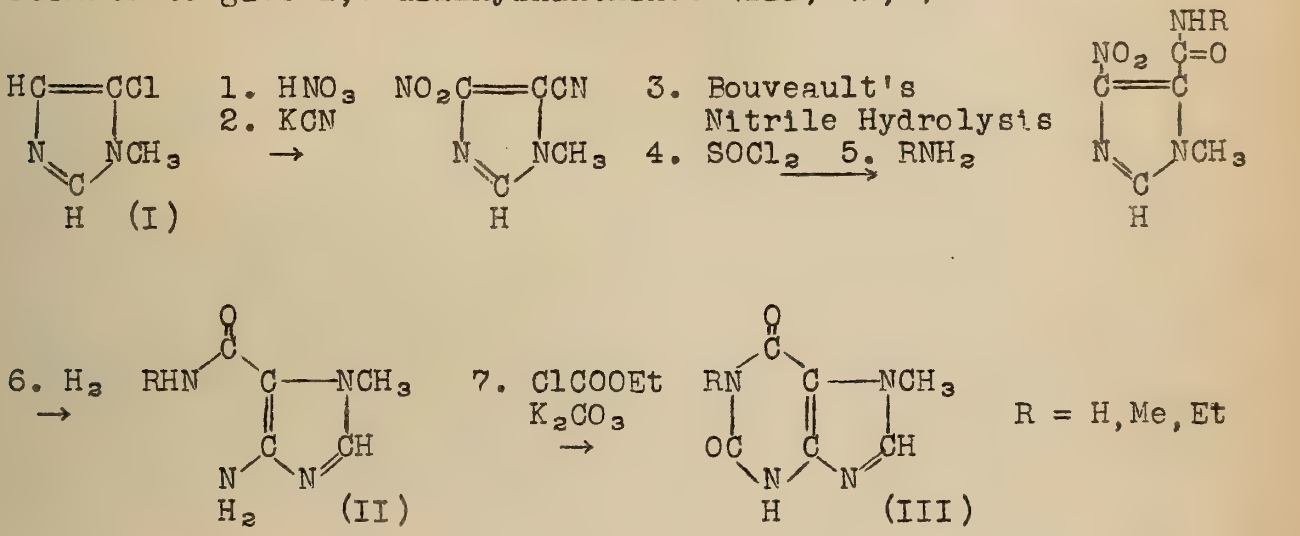
A NEW SYNTHESIS OF PURINES FROM GLYOXALINE DERIVATIVES

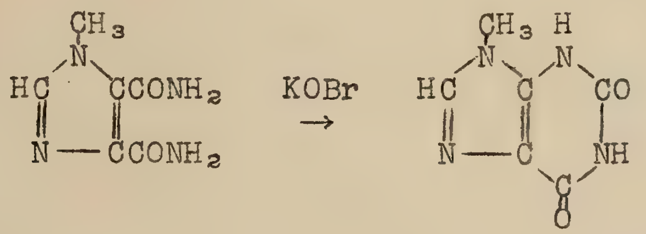
Reported by William C. Hammann October 28, 1949

Interest in the chemistry of nucleosides has stimulated the search for good syntheses of purines. Recent synetheses have built up the purine nucleus by fusing the pyrimidine ring to an already formed imidazole ring.

4-Amino-5-carbamyl-1-methylglyoxaline (II) is built up by standard methods from 5-chloro-1-methylglyoxaline (I). The pyrimidine ring is then completed with ethyl carbonate or ethyl chloroformate to give 1,7-dialkylxanthines (III) (1,2).



The pyrimidine ring may be formed by a Hofmann type reaction on 4,5-dicarbamyl-1-methylglyoxaline (5,6).

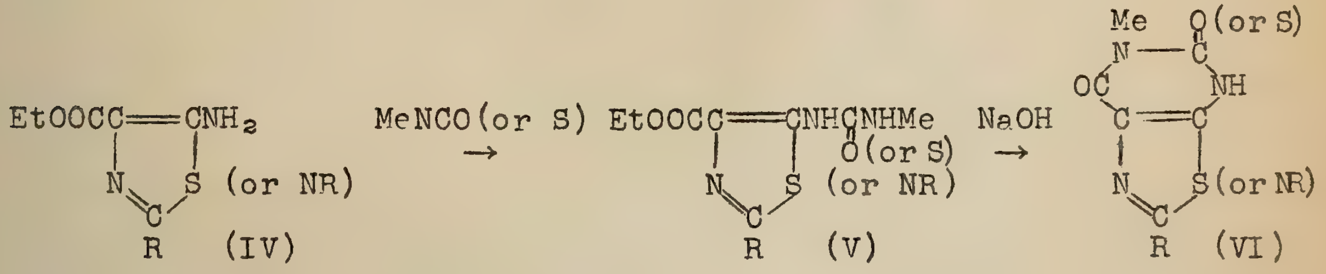


Montecui (4) converted 1-ethyl-2-methyl-4-amino-5-cyanoimidazol to 7-ethyl-8-methylxanthine with urethane and others (3) converted 4-amino-5-carbomethoxyglyoxaline to 4-ureido-5-carbomethoxyglyoxaline with potassium cyanide and cyclized this to xanthine with hydrochloric acid.

None of these reactions are very general and most of them use intermediates which are difficult to prepare. Cook, Heilbron et al (8,9,10) have recently developed a synthesis of purines from gly-

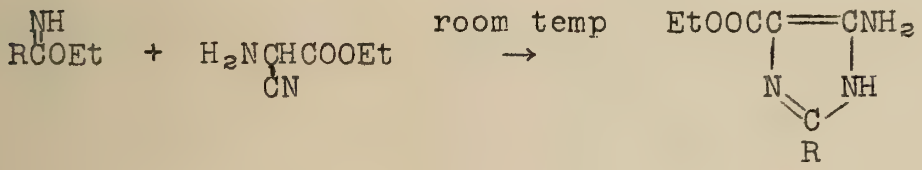
oxaline derivatives which appears to be more flexible than previous ones. Furthermore, it is applicable to the synthesis of thiazolopyrimidines which were previously almost unknown. (For earlier work on thiazolopyrimidines see 11,12,13,14)

In this synthesis a 5-amino-4-carbethoxyglyoxaline or thiazole (IV) is added to methyl isothiocyanate to give a 4-N'-methylthioureido or -ureido-5-carbethoxyglyoxaline or thiazole (V) which is readily cyclized to a 1-methylxanthine or 6-methylthiazolopyrimidine (VI). (R = H,Me).



Synthesis of Glyoxaline and Thiazole Derivatives

To make this a generally useful procedure a general synthesis of 4-amino-5-carbethoxyglyoxalines was developed from the reaction between α-aminonitriles and iminoethers.

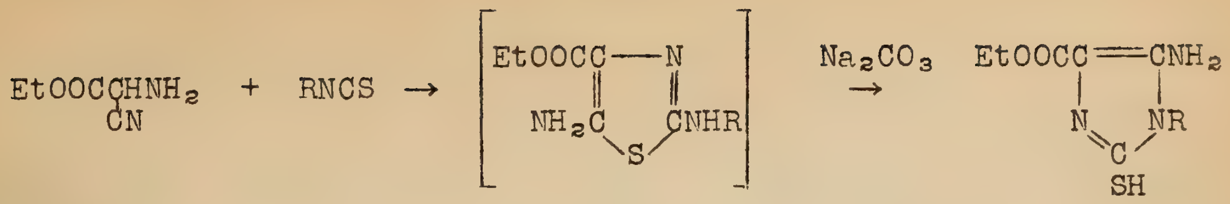


R = H, Me, phenyl, benzyl.

The best preparative results were obtained with α-aminonitriles and thioiminoethers.

R = benzyl 44% yield
R = phenyl 50% yield
R = methyl

Glyoxalines with a 1-alkyl group can be readily prepared from α-aminonitriles and alkyl isothiocyanates under the influence of mild alkali (15).

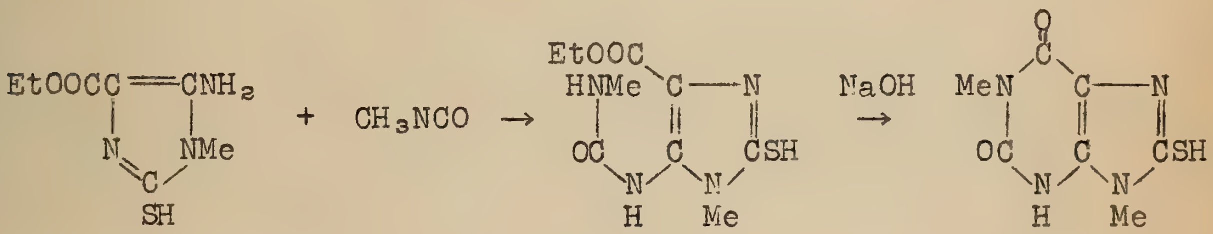


The preparation of 5-aminothiazoles was discussed in a previous seminar (16).

Formation of the Pyrimidine Ring

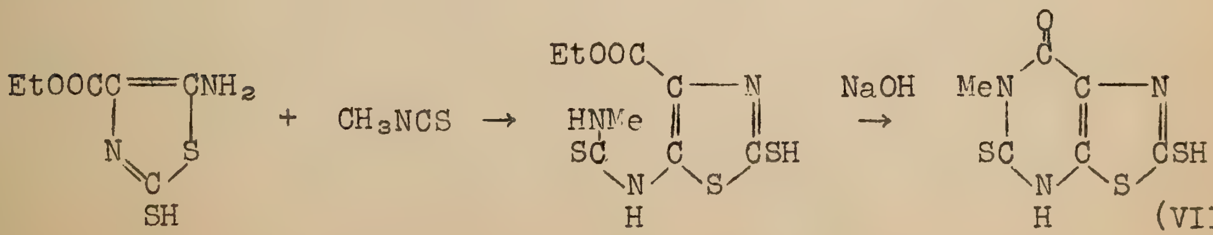
Having access to a variety of imidazole and thiazole derivatives, the formation of the pyrimidine ring by the method of Cook and Heilbron leads to a number of xanthine or thiazolopyrimidine derivatives. The reaction of methyl isothiocyanate with the imidazole or thiazole derivative was carried out by boiling the reactants 1-2 hours in pyridine. The cyclization was effected by warming the ureido compound in 2-5% sodium hydroxide or pyridine. When the cyclization took place in pyridine, it was in several cases possible to carry out the formation of the pyrimidine ring in one step.

Synthesis of a 9-alkyl purine (9).



1,9-dimethyl-8-thiouric acid

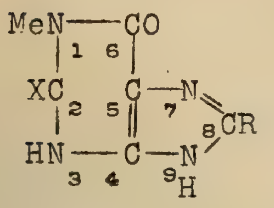
Synthesis of a thiazolopyrimidine (8).



(VII)

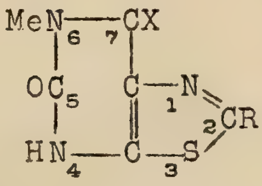
(VII) is 2-mercapto-7-keto-5-thio-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-d]pyrimidine.

A number of other purines and thiazolopyrimidines were prepared by Cook and Heilbron.



X = S; R = H, Me, phenyl, benzyl.

X = O; R = Me, phenyl



X = S; R = SH, H, SMe, benzyl

X = O; R = NHMe, NHCOOEt.

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THE REACTIONS OF EPOXY COMPOUNDS WITH ALCOHOLS

Reported by Thomas G. Miller October 28, 1949

It has long been known that alcohols react reacily with epoxy compounds in the presence of acids or bases to give β-hydroxy-ethers.

$$R_1OH + R_2\text{-}\overset{\frown O \frown}{CH\text{-}CH}\text{-}R_2 \rightarrow R_2\text{-}\underset{}{\overset{OR_1}{CH}}\text{---}\overset{OH}{CH}\text{-}R_3$$

If R_1 and R_2 are alike only one product will result, but if R_1 and R_2 are unlike two isomers may be formed, depending upon which carbon in the ring is attacked. It has been stated that, as a rule, the compound is formed in which the hydroxyl group is attached to the most substituted carbon atom (1). Recently, however, several quantitative studies have been made which indicate that the product formed depends upon the type of catalyst used, acidic or basic, and also upon the nature of the groups adjacent to the oxirane ring (1,2,3,4,5,6).

A mechanism has been proposed which explains the directive influence of substituents and of acidic and basic catalysts upon reaction with alcohols and other nucleophilic reagents (1,2,3,4). In basic solution attack occurs by the RO^- ion which would be directed toward the center of lowest electron density. Thus with the compound $R\overset{\frown O \frown}{CH\text{-}CH_2}$ were R- is any electron donating group, the secondary carbon would have an induced negative charge and the primary carbon a positive charge. The RO^- ion would accordingly attach itself to the primary carbon, giving a secondary alcohol and primary ether. If R- were electron attracting the reverse would be true and the secondary ether would be formed.

In acid solution the following reaction occurs with subsequent weakening of both C-O bonds.

$$R_1 \rightarrow \underset{\ominus\ \ \oplus}{\overset{\frown O \frown}{CH\text{-}CH_2}} \xrightarrow{H^+} R_1 \rightarrow \underset{\ominus\ \ \oplus}{\overset{\frown \overset{+}{O}\text{-}H \frown}{CH\text{-}CH_2}} \xrightarrow{ROH} R_1\text{-}\overset{OR}{CH}\text{-}CH_2OH + H^+$$

If R- were electron donating as shown above, the secondary carbon would have an induced negative charge and the primary carbon a positive charge. The bond between the secondary carbon and oxygen would be most weakened, resulting in cleavage at this spot and formation of the secondary ether. If R- were electron attracting, however, the reverse would again be true and the primary ether would be formed. As might be suspected, the preponderance of one isomer is not as great as in the base catalyzed reaction, since nucleophilic attack could occur on the terminal carbon when the ring is closed. In an uncatalyzed reaction the inductive effect of R- is the only directive influence (2,3).

Chitwood and Fruers reacted propylene oxide with ethyl, isopropyl, n-butyl, and octyl alcohols and in every case the results confirmed the above mechanism (3). Best yields (ca. 80%) were obtained by using a basic catalyst, the primary ether being formed since CH_3- is electron donating. Similar results were obtained with propylene oxide by Petrov using methyl, ethyl, and n-propyl alcohols (5,6), by Swern using allyl alcohol (2), and by Reeve and Sadle using methyl alcohol (7). Hydrolysis reactions proceed in similar fashion. Inversion occurs in the acid hydrolysis of optically active propylene oxide, showing that the secondary carbon is attacked. No inversion occurs during alkaline hydrolysis (8,9).

When a powerful electron donating substituent is present, a unimolecular ring opening may occur (1,2,4,10,11). In an acidic solution the ring opening is aided by the attached proton which weakens the C-O bonds.

$$\underset{\text{I}}{CH_2{=}CH \rightarrow \underset{\underset{H^+}{O}}{\underbrace{\overset{\ominus\quad\oplus}{CH{-}CH_2}}}} \xrightarrow{H^+} \underset{\text{II}}{CH_2{=}CH{-}\underset{+}{CH}{-}CH_2OH} \xrightarrow{ROH} \underset{\text{III}}{CH_2{=}CH{-}\underset{OR}{CH}{-}CH_2OH} + H^+$$

The carbonium ion II may be stabilized by resonance.

$$\underset{\text{II}}{CH_2{=}CH{-}\underset{+}{CH}{-}CH_2OH} \leftrightarrow \underset{\text{IV}}{\underset{+}{CH_2}{-}CH{=}CH{-}CH_2OH}$$

Supporting evidence is given by the fact that crotonaldehyde, which would result from disproportionation of II, and a product formed by reaction of IV with the alcohol have both been isolated from a reaction mixture (4). Similar results have been obtained with other compounds (1,11). There is also evidence which indicates that the ring opening may occur in basic solution. In the base catalyzed reaction of allyl alcohol with 3,4-epoxy-1-butene, Swern obtained a 60% yield of the secondary and none of the primary ether. He explained this anomalous result by postulating the following ring opening (2).

$$CH_2{=}CH \rightarrow \underset{O}{\underbrace{\overset{\ominus\quad\oplus}{CH{-}CH_2}}} \rightarrow CH_2{=}CH{-}\underset{+}{CH}{-}CHO^- \xrightarrow{RO^-} CH_2{=}CH{-}\underset{OR}{CH}{-}CHO^-$$

A mixture of isomers is also obtained by the reaction of methyl alcohol and 3,4-epoxy-1-butene, whereas an almost quantitave yield of the primary ether would be expected (1,4).

The phenyl group can be either electron donating or attracting (2). Styrene oxide reacts as though the phenyl group were electron attracting, giving the secondary ether in basic solution and the primary ether in acid solution (2,12,12).

$$\overset{\oplus}{C_6H_5}\leftarrow\overset{\ominus}{CH}-CH_2(-O-) \underset{OH^-}{\xrightarrow{RO^-}} C_6H_5\underset{OR}{CH}-CH_2O^-, \qquad C_6H_5\leftarrow CH-CH_2(-\underset{H^+}{O}-) \underset{H^+}{\xrightarrow{ROH}} C_6H_5\underset{OH}{CH}-CH_2OR + H^+$$

Epichlorohydrin, $ClCH_2CH-CH_2$ (with O bridging), reacts as expected, considering the electron attracting nature of the $ClCH_2-$ group. The primary ether is formed in good yield in acid catalyzed reactions (2,11). Basic catalysts could not be used in this case, since the chlorine is very easily removed.

When allyl alcohol is reacted with glycidol, $HOCH_2CH-CH_2$ (with O bridging), a primary ether is the major product regardless of the catalyst used (2). Swern suggested that the $HOCH_2-$ group attracted electrons strongly enough to open the ring and form the following ions.

$$HO-CH_2-\underset{OH\ +}{CH}-CH_2 \qquad\qquad HOCH_2-\underset{O-\ +}{CH}-CH_2$$

Acid — Base

In either case a nucleophilic agent would attack the terminal carbon atom, forming a primary ether.

An alternate mechanism has been proposed which differs from the one given above chiefly in that the inductive effect of substituent groups is discounted (14). In a base catalyzed reaction the terminal carbon is attacked because of steric factors. In acid catalyzed reactions carbonium ion formation occurs with the positive charge on the non-terminal carbon atom because of ~~less~~ more hyperconjugation at that position. A mixture of isomers would then result from the two reactions given below.

$$CH_3-\underset{+}{CH}-CH_2OH + ROH \xrightarrow{H^+} CH_3-\underset{OR}{CH}-CH_2OH + H^+$$

$$CH_3-CH-CH_2(-\underset{H}{O^+}-) + ROH \longrightarrow CH_3-\underset{OH}{CH}-CH_2OR + H^+$$

This mechanism is not in agreement with results published on the reaction of styrene oxide with alcohols. According to the above scheme a primary ether should be formed in basic solution and a secondary ether in acid solution. The latter seems especially probable since the carbonium ion would be stabilized by resonance with the benzene ring. This was predicted by Kadesch (1). Although several reports have been published on this reaction, the results are open to question. In one case no structure proof was given (12). In another a completely inadequate structure proof was used (13).

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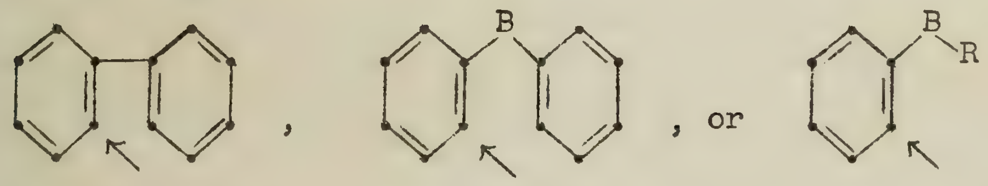
A NEW METHOD FOR THE SYNTHESIS OF NITROGEN HETEROCYCLES

Reported by Seemon H. Pines October 28, 1949

The Waterman and Vivian reaction (10, 11) is a new type reaction used in the synthesis of various heterocyclic compounds having at least one nitrogen in the ring. One of the advantages of this reaction is that one or more complete steps in the previous methods of making some of these compounds is eliminated, thus reducing large scale production costs. Good yields of product are generally obtained, which are easily and inexpensively recovered from the reaction mixture.

Many of the previously used methods for ring closures for nitrogen heterocycles involved nitration, reduction to the amine, followed by an oxidative ring closure on the amine nitrogen, by PbO, for example. The amino group must be ortho to the bridge linkage, indicated below where B is the bridging atom, or atoms.



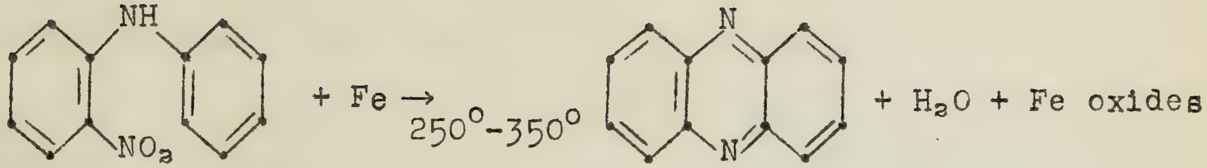
This new reaction employs a suitable oxygen acceptor and an ortho-nitro-compound, mixed together at reasonably high temperature in a dry state, or with an inert diluent.

The oxygen acceptor must be one that will not aminize the nitro radical. The patent issued to Waterman and Vivian (11) indicates that Fe, Pb, C, P, and a number of other elements may be used as reductants.

Slack and Slack, investigating the same reaction, (6) concur with the inventors, that the various substituents present in either or both of the carbon-containing radicals joined by the bridge-linkage do not interfere with the reaction with the exception listed under type B below. Alkyl, aryl, alkoxy, halogen, nitro and amino groups do not prevent the reaction, provided there is a free ortho position.

The mechanism of these reactions is not known. Five illustrations show the variations in the reaction.

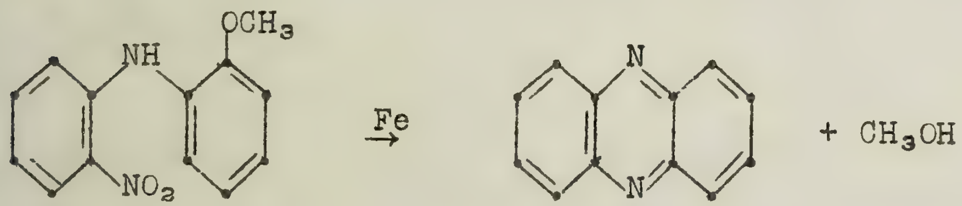
A. Reactions involving elimination of oxygen and the elements of water.



Phenazine

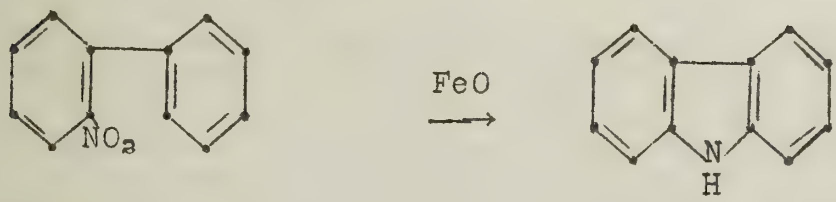
The oxides of iron were not analyzed. It was found that: 1.) Addition of dehydration agents was ineffective; 2.) Additional nitro groups made the reaction quite violent unless an inert diluent was used (e.g. 2,4-dinitrodiphenylamine and 2,4-dinitro-4'-hydroxydiphenylamine).

B. Reactions in which a substituent is eliminated.

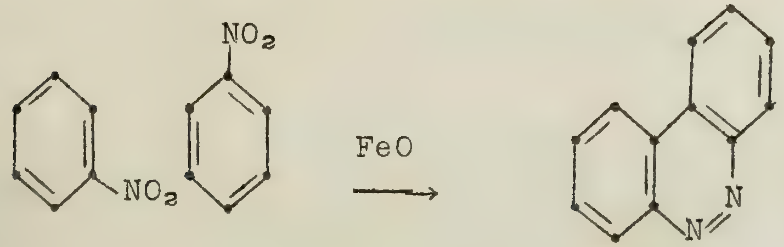


It was observed that a 2-alkoxy group was eliminated in preference to a hydrogen. Thus, to produce the 1-alkoxyphenazine, the alkoxy group must be on the same ring as the nitro group. From 2,2'-dinitrodiphenylamine, using no diluent, was produced a 30% yield of unsubstituted phenazine.

C. Use of ferrous oxalate as the catalyst. Carbazole in good yield resulted from the treatment of 2-nitrobiphenyl with anhydrous ferrous oxalate.



D. Bimolecular type reductive ring closure.

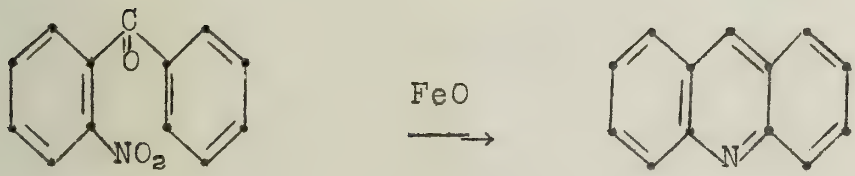


3,4-benzocinnoline

This type reaction provides a synthesis for benzocinnolines. The reaction is carried out in the same manner as the others above.

E. Ring closure involving removal of carbonyl oxygen as well as nitro-oxygen.

2-methylbenzimidazole

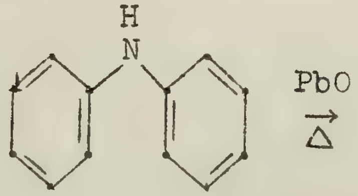
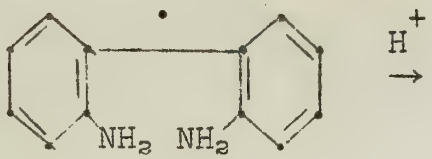
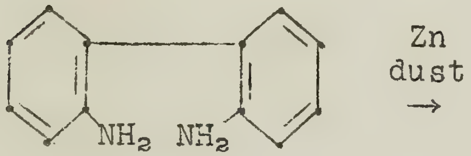
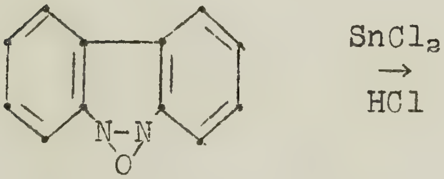
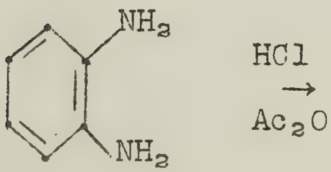
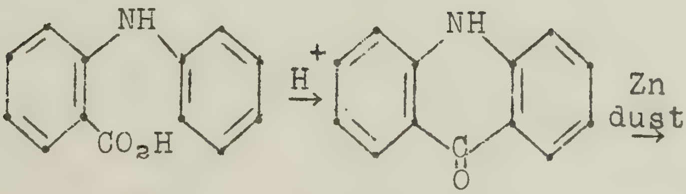
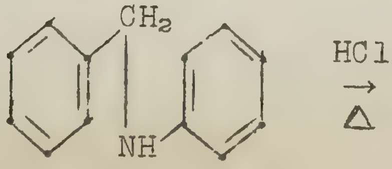


Acridine

The manner in which the reaction is carried out is quite simple, and can be described essentially by the following preparation of phenazine.

Five grams of ortho-nitrodiphenylamine was intimately mixed with 25 grams of iron filings and heated at a temperature of about 250° to 350° C. for ten to fifteen minutes. Upon completion of the reaction the phenazine was sublimed out of the mixture. The sublimate was nearly pure phenazine, and represented a yield of approximately 73% of theory.

A comparison of the Waterman and Vivian reaction with other methods of preparations of the same type compounds is shown below.

Product	W. + V. yield	Other prep.	Yield	Ref.
Phenazine	73%		.5%	(1)
Carbazole	80%		90%	(7)
3,4-Benzo-cinnoline	46%		45%	(5)
				
				(8)
2-Methyl-benzimi-dazole	42%		60%	(4)
Acridine	good		70%	(3)
			-	(2)

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RECENT DEVELOPMENTS IN NITROAMINE CHEMISTRY

Reported by Ernest D. Nicolaides November 4, 1949

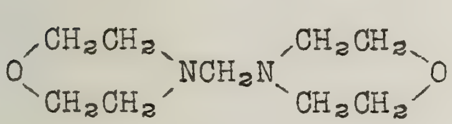
Introduction.

Interest during the last war on the nitration of hexamethylenetetramine to RDX (1,3,5-trinitrohexahydro-1,3,5-triazine) (III, n=1) has resulted in an increased knowledge of nitroamine chemistry. The catalyzed nitration of amines has already been discussed (1), but other developments have taken place since then which may lead to an understanding of the mechanism of the nitration of hexamine to RDX.

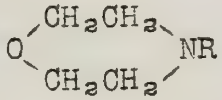
I. Nitration of Some Methylenediamines, Methylenebisamides and Aminomethylnitroamines.

Chapman (2) has nitrated methylenediamines of the type IV. In general, nitration of compounds like IV gave aromatic or ill defined products. Nitration of compounds like V gave RDX or its homologs depending upon n. Nitration is best effected using 98% nitric acid, acetic anhydride and ammonium nitrate at 55-75°.

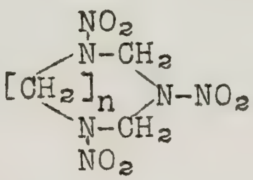
Compound	Products
I	III (n=1) and II ($R=NO_2$)
IV (R=R'=Me)	III (n=1) and Dimethyl Nitroamine
V (n=2, R=Morpholino)	III (n=2) and II ($R=NO_2$)
IV (R=Me, R'=Ph)	p-N-dinitro-N-methyl aniline
V (n=3, R=Morpholino)	III (n=3) and II ($R=NO_2$)
V (n=4, R=Morpholino)	Water insoluble oil
IV ($R=R'=CH_2CH_2ONO_2$)	No reaction



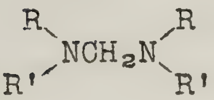
I



II



III



IV

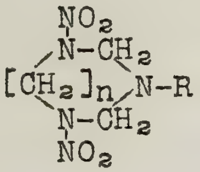
$CH_2RN(NO_2)[CH_2]_nN(NO_2)CH_2R$

V

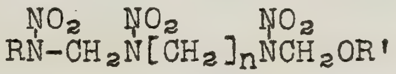
The nitration of a number of methylenebisamides and related compounds of the type NHRCHR'NHR where (R=Ac; R'=H, Me or Ph);

(R=CO_2Et; R'=H or Me) and (R=$CONMe_2$; R'=H) was carried out (3). The most common reaction seemed to be cleavage of the N-C-N linkages, but methylenebis-N-acetamide (R=Ac; R'=H) was unaffected by cold nitric acid. Addition of acetic anhydride to the last reaction gave the compound $NO_2NAcCH_2NAcNO_2$ which can be hydrolyzed to methylenedinitroamine with aqueous ammonia.

The nitration of aminomethylnitroamines is generally successful (4). 1,5-Dinitro-3-alkylhexahydro-1,3,5-triazines VI (n=1; R=Me or Et) on treatment with 98% nitric acid at 10° give the linear nitrate esters, VII (R=Me or Et; R'=NO_2), while treatment with nitric acid, acetic anhydride, acetic acid and ammonium nitrate gives RDX. Compounds of the type VI (n=2; R=Me, Et, Pr, Bu or cyclohexyl) give the corresponding linear compounds without ammonium nitrate and both the linear and ring compounds with ammonium nitrate. From the evidence available one cannot predict what the products will be, but in no case has RDX and its homologs been obtained without using ammonium nitrate.



VI



VII

II. The Reaction of Nitroamines with Formaldehyde.

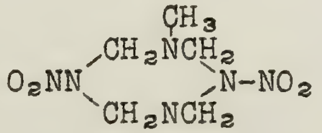
It has previously been thought that nitroamines will not react with formaldehyde in the absence of bases (5), but it has recently been shown (6) that ethylenedinitroamine, VIII (n=2; R=H) condenses with 40% formaldehyde to form N-hydroxymethylethylenedinitroamine, IX (R=CH_2OH). This compound reacts with morpholine to give a derivative, IX (R=morpholinomethyl), but with an excess of morpholine and formaldehyde the compound VIII (n=2; R=morpholinomethyl) is formed instead. These morpholino derivatives can be accurately titrated with 0.1N NaOH.

Treatment of ethylenedinitroamine with excess piperidine and formaldehyde produces VIII (n=2; R=piperidinomethyl), but diethylamine and methylaniline fail to form any crystalline products. Tri- and tetra-methylenedinitroamine, VIII (n=3 or 4; R=H) condense with formaldehyde to give the diols, VIII (n=3 or 4; R=CH_2OH) which also form characteristic morpholine derivatives.

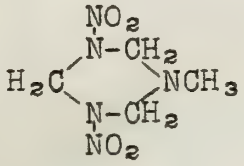
$NO_2NR[CH_2]_nNRNO_2$ $\quad\quad$ $NO_2NRCH_2CH_2NHNO_2$

VIII $\quad\quad$ IX

Nitroamines also react with formaldehyde and primary or secondary amines (7). When methylenedinitroamine in ethyl acetate is treated with dry formaldehyde and then with an alcoholic solution of methylamine, X results, but if 40% aqueous formaldehyde is used the product is XI.



X

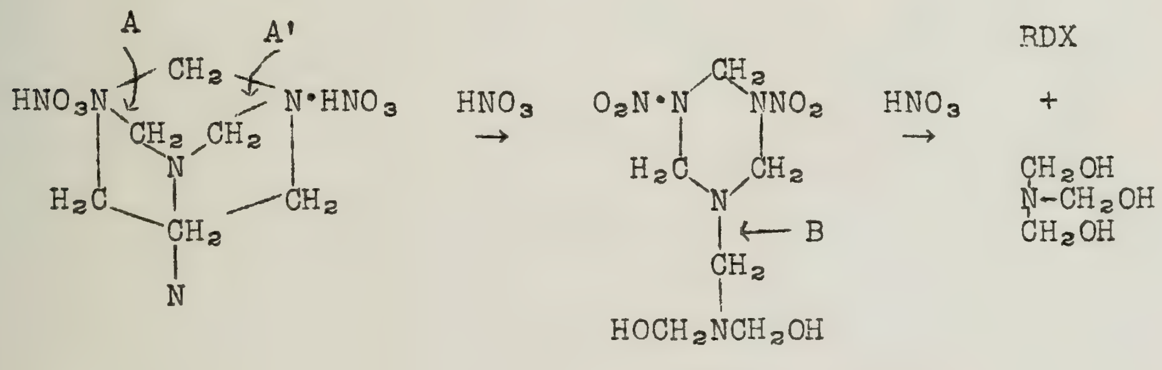


XI

III. <u>Mechanism of the Nitration of Hexamine to RDX</u>.

Both a fragment and a stepwise mechanism can be postulated for the formation of RDX from hexamine since the hexamine molecule has C-N-C links and the product also has C-N-C links and is symmetrical. In the formation of several homologs of RDX it has been suggested that the combination of fragments to form a single cyclic, unsymmetrical product would be remote, but to apply this argument to RDX is unreasonable.

The stepwise mechanism proposed is that cleavage at A and A' occurs in the hexamine dinitrate molecule to give XII. This is then cleaved at B to give RDX and trimethylolamine. None of the intermediates have been siolated, but there is evidence for their existence (8) (9) (10).



XII

However, in the Bachmann method for preparing RDX, two moles of RDX are formed from one mole of hexamine (11). The only explanation for this is a fragment mechanism from the by-products of the first mole of RDX formed.

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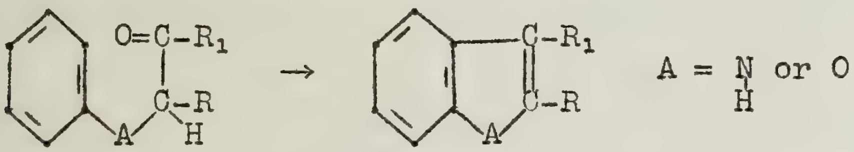
BENZOTHIOPHENES AND HIGHER POLYCYCLIC DERIVATIVES

Reported by George Speranza November 4, 1949

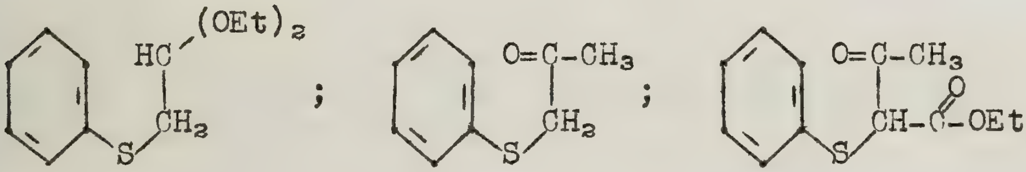
Benzothiophenes may be used as starting materials for the synthesis of pharmaceuticals and as a precursor of thioindigo. Synthesis of this class of compounds has consequently been stimulated.

Older methods of preparation are reduction (1) of thioindoxyl derivatives[1] or (2) of the benzothienyl ketones obtained by acylation of benzothiophene.[2] The first method is not of general use owing to the difficulty of preparing thioindoxyl compounds and the poor yields obtained on reduction. Benzothiophene can be obtained (1) from coal tar, (2) by synthesis from styrene and hydrogen sulphide,[3] (3) from o-ethylthiophenol.

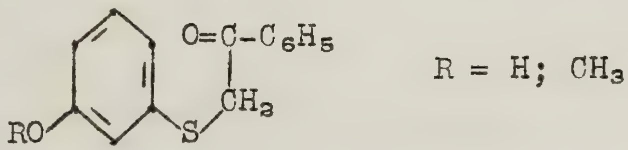
Coumarones and indoles can be obtained by cyclodehydration of arylketoethers and arylketoamines:[4]



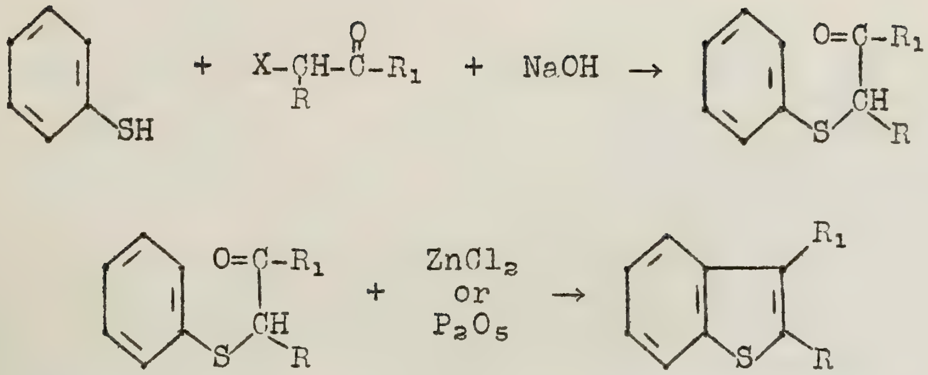
Analogous preparations of benzothiophenes failed to give the desired products in three cases indicated below.[5] This failure was



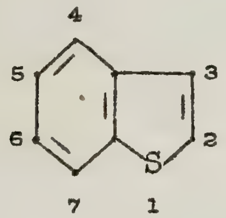
attributed partly to the poor activating influence of the sulphur group and partly to the ease by which the arylketosulphides are converted into aryldisulphides. The activating influence of the methoxy and hydroxy groups permit cyclizing to take place.[6]



This method was recently investigated by Werner[7] and found to be general.

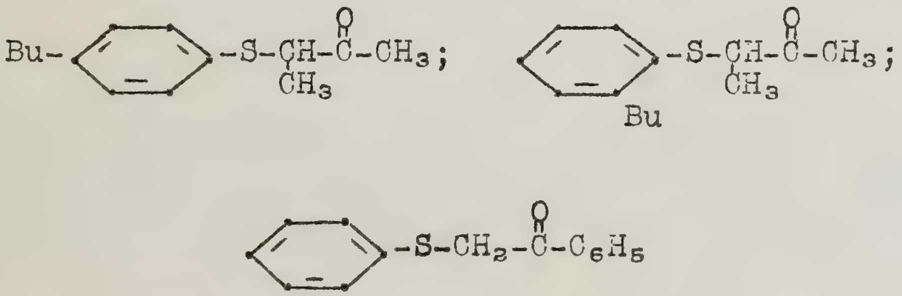


Werner was able to prepare the following compounds in almost quantitative yields. I, 3-methylbenzothiophene; II, 2,3-dimethylbenzothiophene; III, 2,3,5-trimethylbenzothiophene; IV, 2,3,7-trimethylbenzothiophene; V, 2,3-dimethyl-α-naphthothiophene; VI, 2,3-dimethyl-β-naphthothiophene. The numbering is illustrated below.

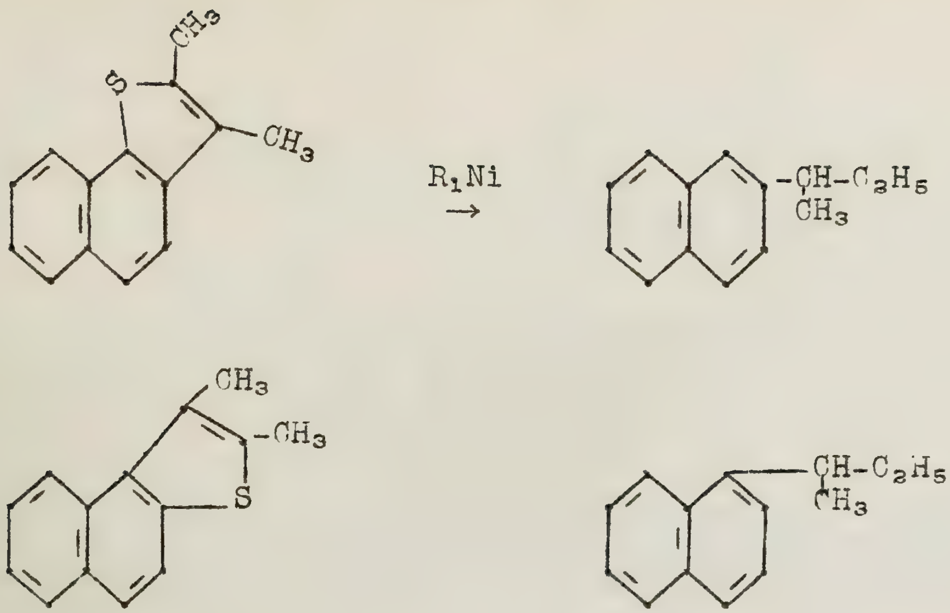


Too little caustic in the reaction mixture gave rise to the formation of large quantities of aryldisulphides which are not stable to hydrohalic acids.

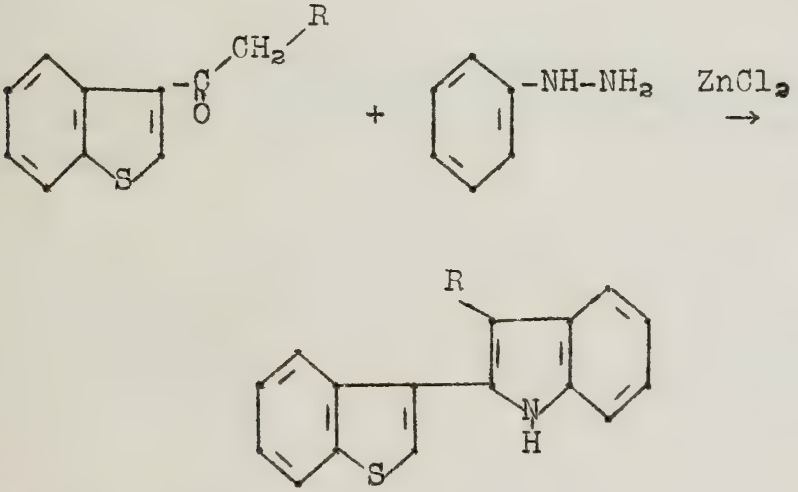
Cyclodehydration will not take place if the <u>ortho</u> position to the sulphur atom is deactivated. The three following compounds were resistant to cyclization.



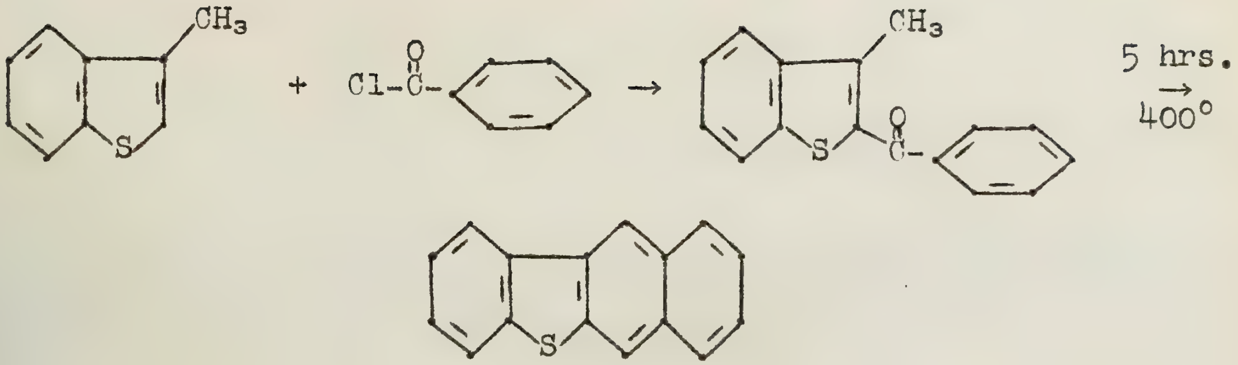
The structure of compounds V and VI were proven by reductive desulphurization with Raney nickel.



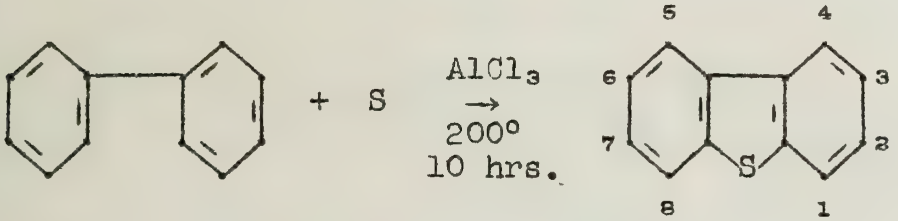
The most interesting reaction of the benzothiophenes is the formation of acyl ketones in the 3 position which are prepared by the Friedel and Crafts reaction. They undergo reactions of typical aryl alkyl ketones and have been used in the Fischer Indole Synthesis to join the benzothiophene to the indole ring.[8]



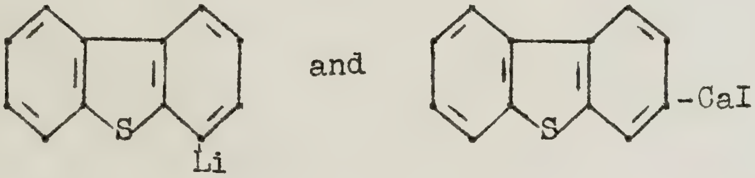
If the 3 position is already substituted by an alkyl group the next point of attack by an acid chloride is in the 2 position. This was proven[9] by carrying out the Elbs reaction which on these compounds leads to polycyclic nuclei in which thiophene is one of the rings.[10]



Dibenzothiophene has been extensively studied.[11] It is prepared from sulphur and biphenyl in about 60% yields. Halogenation, nitration, sulfonation and the Friedel and Crafts reactions occur

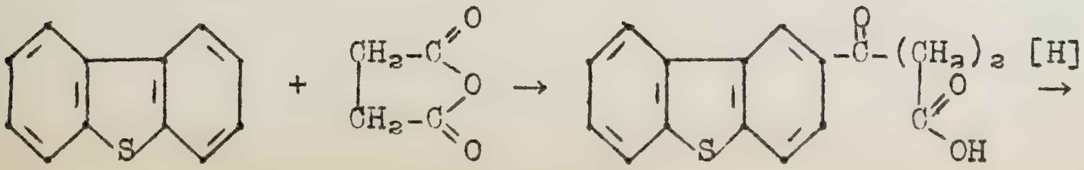


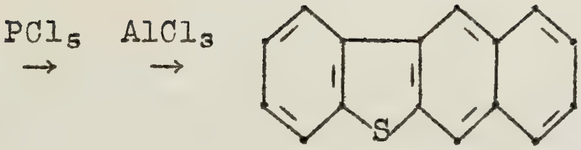
in the 3 or 6 position and disubstitution gives the 3,6 disubstituted compound. Butyllithium and phenylcalciumiodide give the compounds below, thus opening the way for substitution in the one and two positions.



The 4-position must be activated from the 1-position in order to obtain substitution in the 4-position.

By employing the Friedel and Crafts reaction, and the Elbs





reaction (for both structure proof and synthesis) the synthesis of many polycyclic compounds - one ring of which is the thiophene nucleus - has become possible.

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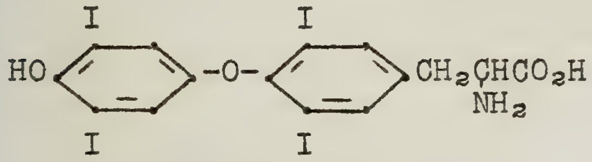
A NEW SYNTHESIS OF THYROXINE

Reported by John C. Wright November 4, 1949

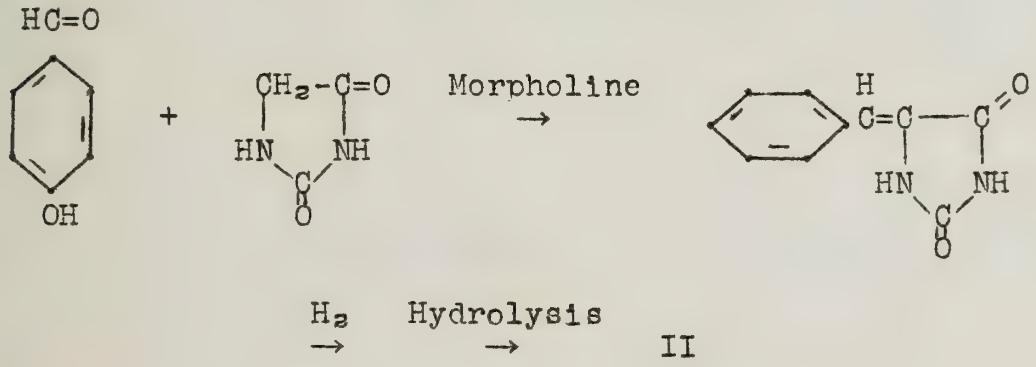
Thyroxine (I) is the active principle of the principal endocrine secretion of the thyroid gland. Methods for its isolation and synthesis are already available (1,2,3), but use of it has never become widespread although it is known to be highly active physiologically. This is largely due to the difficulties involved in its synthesis. Work has recently been conducted in England to improve this synthesis.



I

II

Since tyrosine (II) is important in many syntheses of thyroxine, a satisfactory synthesis of this intermediate was most desirable (4). The best method found was the condensation of p-hydroxybenzaldehyde with hydantoin using morpholine as the catalyst. Subsequent hydrogenation of the olefinic bond followed by hydrolysis of the p-hydroxybenzylhydantoin gave tyrosine in an overall yield of 55%.

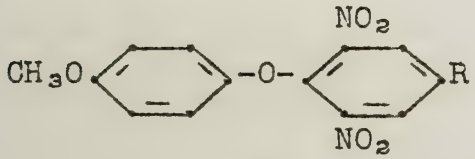


Tyrosine was iodinated by treatment with ICl in hot concentrated HCl. The diiodo product was obtained in 86% yield (4).

The workers attempted unsuccessfully the diiodination of diphenyl ethers with the idea of proceeding from there to produce thyroxine (4). Since it was known that activated halobenzenes condense with phenols to give substituted diphenyl ethers, use of this reaction was made to produce such ethers in which iodine or groups which could be converted to it were already present. Harington and

Barger (3), in the best synthesis of thyroxine to date, used 3,4,5-triiodonitrobenzene and hydroquinone monomethyl ether to give a diiododiphenyl ether. In their procedure the nitro group was then reduced and the amine function replaced by CN. This nitrile was converted to the aldehyde, which upon condensation with hippuric acid, reduction, hydrolysis and further iodination gave thyroxine.

The British workers considered that a 2,6-dinitrodiphenyl ether (III) was a better type intermediate in the synthesis. They reduced the two nitro groups, and the diamine thus formed was converted to the diiodide through tetrazotization under anhydrous conditions using nitrosyl sulfuric acid (4,5). Harington and Barger had previously failed in all attempts at this conversion.



(R = CH_3, CO_2CH_3, CHO)

III

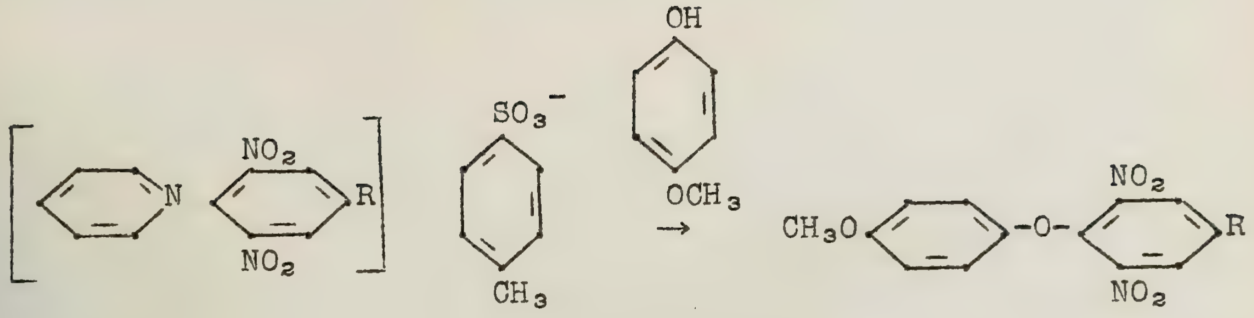
The practicability of the above approach established, the English workers sought a method of preparing dinitrohalobenzene compounds. The corresponding dinitrophenols were the obvious starting points. It was known that chlorodinitrobenzenes can be made from dinitrophenols by the Ullmann and Nadai procedure (IV) (6,7,8,9).

ROH +  $\rightarrow ROSO_2C_6H_4CH_3 \xrightarrow{\text{Pyridine}} [RNC_5H_5]^{+} + [SO_3C_6H_4CH_3]^{-}$

IV

$\xrightarrow{HCl} RCl + C_5H_5N, HO_3SC_6H_4CH_3$

A study of this reaction suggested that a phenol could be substituted for the mineral acid used in the last step. The following results were obtained (10):



$$+ \quad C_5H_5N, \ HO_3SC_6H_4CH_3$$

$$(R = CH_3, \ CO_2CH_3, \ CH_2CH_2CO_2C_2H_5, \ CHO)$$

The reaction was also found to be valid when benzenesulfonyl chloride and also 2,6-dinitrohalobenzenes were used. Activating nitro groups are necessary in the reaction.

In the final steps of the synthesis it seemed that condensation of 3,5-diodo-4(4'-methoxyphenoxy)-benzaldehyde with hippuric acid could give a desired intermediate. Yields of the reaction were low and when the corresponding 3,5-dinitro compound was used it could not be reduced successfully to the diamine. Attempts to use hydantoin as illustrated previously resulted in cleavage of the ether.

The following overall procedure was used: p-hydroxybenzaldehyde was condensed with hydantoin and the product reduced. The hydroxybenzylhydantoin was then nitrated to give the dinitro compound in 83% yield. This dinitrophenol upon treatment with p-toluenesulfonyl chloride, pyridine and then hydroquinone monomethyl ether gave the diphenyl ether. This could be reduced and the amino group replaced by iodine using the procedure described earlier. Upon hydrolysis the amino acid was obtained. Further iodination gave thyroxine in a yield of 14% based upon p-hydroxybenzaldehyde (11).

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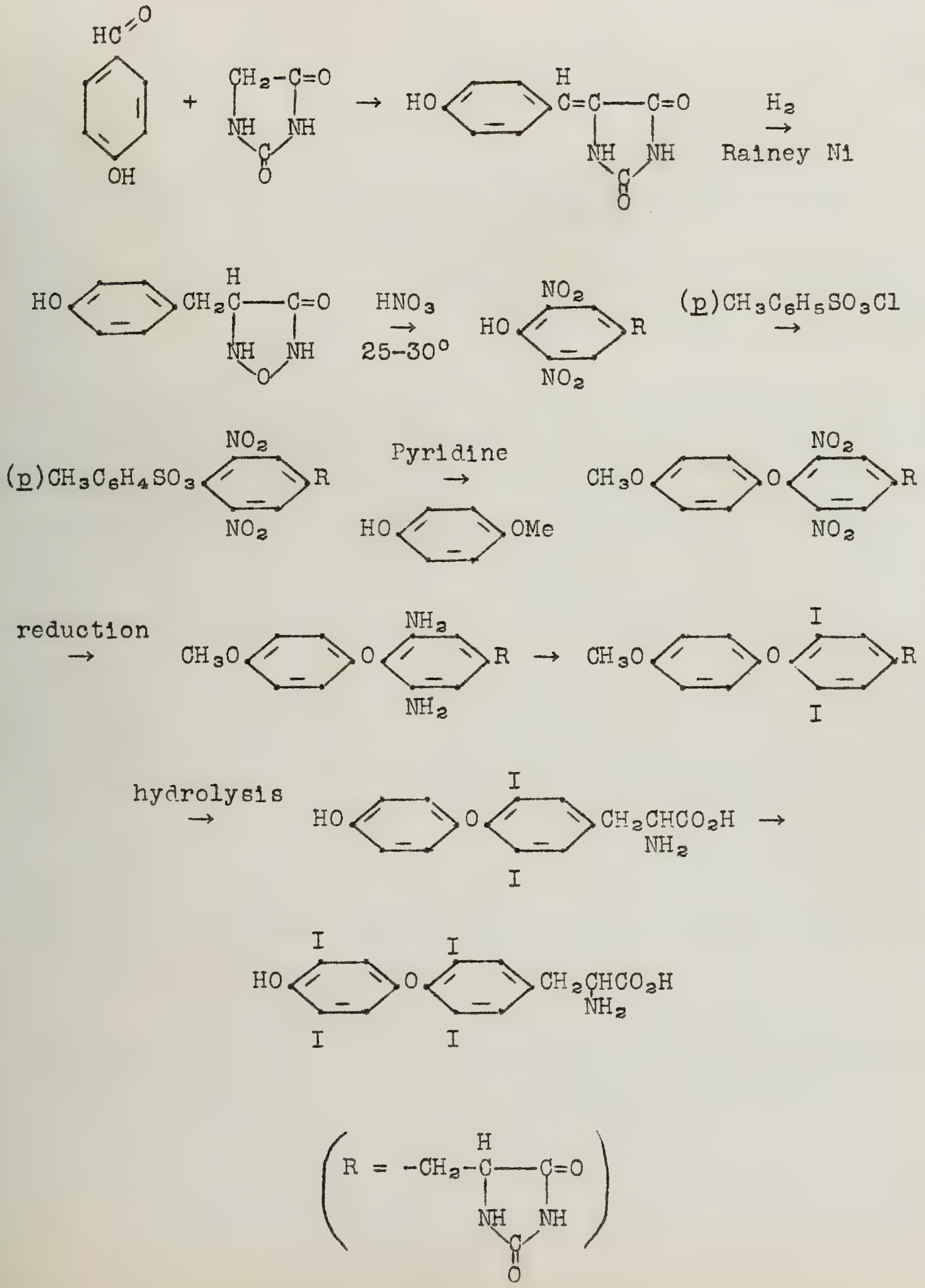
Synthesis of thyroxine beginning with p-hydroxy benzaldehyde:



POLYNITRO MOLECULAR COMPOUNDS

Reported by John Figueras November 11, 1949

Introduction: Any theory which is proposed for complex formation between polynitro aromatic compounds and other aromatic compounds must take into account the following facts: a) reaction is accompanied usually by a color change; b) X-ray studies indicate that all molecules in the complex are at distances greater than 3 A. : this precludes covalent bond formation (1,2,3,4); c) the effects of substituents must be accounted for; d) complexes are formed instantaneously in practically all cases.

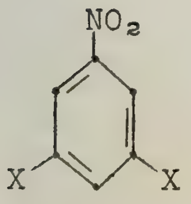
General Information: To simplify nomenclature, we will designate the electron-poor polynitro compound as the acceptor, and the other constituent, which is electron-rich relative to the nitro compound, as the donor.

In general, electron repelling substituents in the donor increase the stability of the complex and have the opposite effect in the acceptor, while electron attracting groups in the donor decrease the stability of the complex and have the opposite effect in the acceptor (5). Shinomiya (6) found that complexes of polynitro compounds with α-substituted naphthalenes decrease in stability with different α-substituents as follows:

$$NH_2 > Me > OH > Et > OMe > Cl > Br > OEt > (H) > COOH > COOMe > -O\phi > CN > -CO\phi > NO_2$$

This is also the order of increasing positivity, exceptions being explained on the basis of steric factors.

Bennett and Wain (7) synthesized compounds of the type:



X = $-COCl$, $-CN$, $-CONH_2$, $-COOMe$, $-SO.Me$, $-SO_2.Me$, $-SOCl_2$

These compounds form complexes with aromatic hydrocarbons. The groups fall into the following sequences of diminishing tendency to promote compound formation: a) $COCl > COOMe > CONH_2$; b) $SO_2Cl > SO_2.Me > SO.Me$; c) $NO_2 > CN > COOMe$. These are also sequences of diminishing electron attraction.

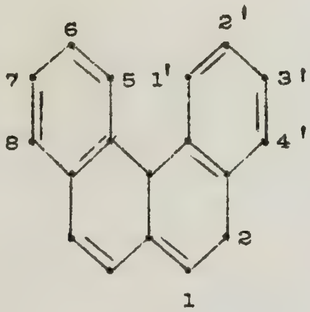
Shinomiya (8) found the following relationships for the complex-forming ability of polynitro compounds:

trinitrobenzenes: sym > asym or vic
dinitrobenzenes: para or meta > ortho
trinitrotoluenes: 2,4,6 > 2,3,4 or 2,4,5

He also found (9) that s-trinitrobenzene formed more stable complexes than any substituted s-trinitrobenzene, regardless of the polar nature of the substituents. These facts are explained on the basis of steric factors.

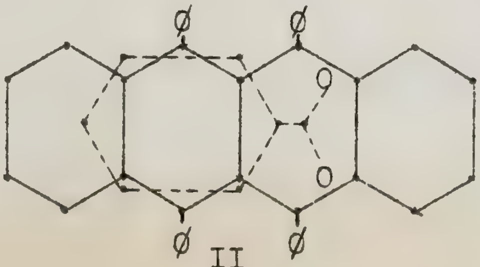
Weiss (5,10) states that molecular compounds become more stable, the greater the extent of conjugation in the donor. Relative to this fact, Briegleb (11) found that the heat of reaction of TNB with stilbene is over five times as great as its heat of reaction with dibenzyl.

Orchin (12,13) found that certain methyl-substituted tetracyclic aromatic hydrocarbons formed either very low melting picrates, or none at all, although their position isomers formed perfectly stable, high melting picrates; e.g., of the six monomethyl 3,4-benzphenanthrenes (I), picrates of all could be



I

prepared except that of the 5-methyl compound. This is explained on the basis of overlap between the 5-methyl group and the 1' hydrogen atom, which forces the benzphenanthrene nucleus into a non-planar configuration, thus increasing the distance through which electrical forces involved in complex formation must act. Bowen and Coates (14) observed that rubrene formed a complex with nitrobenzene in solution, but not with TNB or dinitrobenzene. They suggested that the nitrobenzene molecule can accommodate itself in a plane parallel to the naphthacene center of the rubrene molecule (cf. II), but the polynitro compounds cannot because of interference between the nitro groups and the four phenyl groups.



II

Theories of Complex Formation: Bennett et al (7,15,16) and Hammick and Sixsmith (17) proposed that complex formation involved the formation of a covalent bond. Anderson (18) objected to the theory of Bennett on energetic grounds and because of previous X-ray findings (4). Huse, Powell, and Cook (1) stated flatly, on the basis of their X-ray studies, that all structures involving covalent bond formation are at once excluded from consideration.

Weiss (5,10' suggested that complex formation proceeds by a one electron transfer from the donor to the acceptor, through a transition state:

$$A + B \rightleftarrows (AB)_t \rightleftarrows (A)^{+}(B)^{-}$$

Dewar (19) objected to this theory on the grounds that: a) there is no evidences that one electron transfers take place in organic chemistry unless one of the reactants is a radical; b) the heats of formation of complexes are too low for a salt-like structure; c) an ionic structure would indicate greater stability in polar than in non-polar solvents, whereas the reverse is true.

Powell and Huse (20), on the basis of melting point data (Table I), concluded that intermolecular forces in crystals of molecular compounds are not markedly greater than those found in crystals of the components: an ionic bond would lead to much higher melting points for the complexes.

TABLE I

A	B	m.p. of A	m.p. of B	m.p. of AB
aniline	TNB	-8	122	123
2,4,6-tribromoaniline	TNB	118.5	122	108.5
p-chloroaniline	TNB	71	122	110
3,5-diiodo-p-toluidine	TNB	125.5	122	95.5

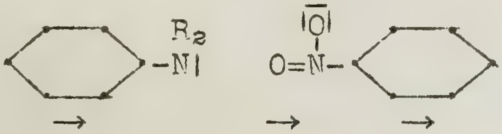
Rapson, Saunder and Stewart (21) found a number of adducts of 4,4'-dinitrodiphenyl in which the ratios of donor to acceptor varied between 3:1 and 5:1. From considerations of crystal structure and the relative sizes of the components, they were able to calculate theoretical ratios of the components in a complex (Table II).

TABLE II

Molecular compounds of 4,4'-dinitrodiphenyl with:	Color	m.p.	Mol. ration of components,obs.	Mol. Ration of components,calc.
4-acetoxydiphenyl	cream	225	5:1	4.6 - 4.9:1
benzidine	red	240	4:1	3.8 - 3.9:1
4-iododiphenyl	pl.yel.	192-220	3.5:1	3.5:1
4-aminodiphenyl	orange	220	3:1	3.4:1

From these data, the authors concluded that the molecular ratio of the components is a function of the size and packing of the components in the crystal, and not of some type of bond, as assumed by Weiss.

Briegleb (11) accounted for complex formation by postulating the induction of dipole moments in the donor by the permanent dipoles resident in the C-N bonds of the nitro compound. These induced dipoles then interacted with the permanent dipoles in the nitro compound to give the complex. Gibson and Loeffler (22) proposed that complex formation was due to the primary electromeric and inductomeric polarizations which attend an electron transfer, without an actual electron transfer, as shown in Figure III.



III

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CYCLIC AND LINEAR "SILICONE" POLYMERS

Reported by Frank B. Hauserman November 11, 1949

"Silicone" polymers are commercially important as lubricating oils and greases, mold lubricants, gaskets, wire coatings, dipping compounds, insulation and so on. The lubricating oils and greases are valuable as they have remarkable stability to heat and oxidation and retain their viscosity over a wide temperatre range.

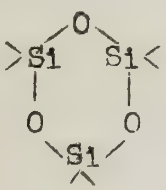
Early work by Kipping (1,2) on disubstituted dichlorosilanes (R_2SiCl_2) was carried out with the idea of obtaining $R_2Si{=}O$ type compounds, analogous to the ketone structure and these compounds were to be called silicones. But hydrolysis of such silanes resulted in linear and cyclic low polymer products only. Further work along this line resulted in the same type compounds and not the theoretical silicones (3,4,5,6). The name silicone is therefore not appropriate from a structural point of view for products obtained by the hydrolysis of R_2SiX_2 compounds. Nevertheless this term is used for all organo-silicon-oxygen polymers being manufactured.

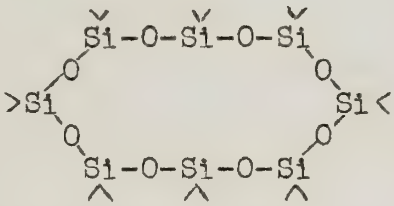
I. PREPARATION

The polymer disubstituted siloxanes can be divided into four general classes: (a) the cyclic members; (b) the open chain polymers with temporary or reactive end groups such as hydroxyl terminated polymers; (c) linear polymers with permanent end groups which show a high relative stability to both heat and moisture; (d) branched chain polymers.

Cyclic Polymers

These polymers contain ring structures of alternate silicon and oxygen atoms with six to twenty members. The nature of these cyclic compounds is represented by I and II.





II

I Hexaalkylcyclotrisiloxane Hexadecaalkylcycloocatasiloxane

a) The hydrolysis of dimethyldichlorosilane (prepared by the action of CH_3Cl on Si (8)) with water results in a mixture of cyclic polymers of the composition $[(CH_3)_2SiO]_x$ where x is three to ten (7). The relative amounts of each polymer depend upon the conditions used, although the tetramer is generally produced in the greatest amount.

b) Hydrolysis of diethoxydimethylsilane (prepared by the action of lithium ethoxide on triethylsilane (9)) gives a mixed polymer fluid which can be separated into a low polymer portion and a non-volatile portion. The low polymer portion is essentially a mixture of cyclic dimethylsiloxane polymers containing four to eight silicon atoms (10).

c) Cyclic low molecular weight polymers may be obtained in yields of 90% by heating dimethylsiloxane polymers at 400° (10).

Linear Polymers

These polymers may vary in their end groups, groups on the silicon atoms, and in their length. They were first described by Kipping (2) and since then a variety has been prepared.

a) Methyl polysiloxanes with trimethylsiloxy end groups.

$$(CH_3)_3SiO\left[\begin{array}{c} CH_3 \\ | \\ Si-O \\ | \\ CH_3 \end{array}\right]_n -Si(CH_3)_3 \qquad \text{III}$$

1) The cohydrolysis of an equal molar mixture of ethoxytrimethylsilane and diethoxydimethylsilane results in a series of polymers of structure III. The polymers contain from two to nine silicon atoms (11). Similar copolymer mixtures may be obtained from the cohydrolysis of chlorotrimethylsilane and dichlorodimethylsilane (12).

2) The catalytic rearrangement of a mixture of cyclic methyl polysiloxanes and hexamethyldisiloxane with a small amount of sulfuric acid results in a series of polymers of formula III (7).

b) Open chain dimethyl siloxanes with ethoxyl end groups (13).

$$C_2H_5O-\left[\begin{array}{c} CH_3 \\ | \\ Si-O \\ | \\ CH_3 \end{array}\right]_n -H_5C_2 \qquad \text{IV}$$

These are preapred by partially hydrolyzing diethoxydimethylsilane. Again, n in IV, as in III, may vary from one to a very large number depending upon the quantity of water used.

c) Polymer siloxanes with active groups on the chain as well as on the terminal groups (14).

$$C_2H_5O-\left[\begin{array}{l} CH_3 \\ | \\ SiO- \\ | \\ OH_5C_2 \end{array}\right]_n-H_5C_2 \qquad V$$

The partial hydrolysis of triethoxymethylsilane with aqueous sodium hydroxide in ethyl alcohol results in a series of polymers of structure V in which n varies from two to five.

d) Open chain polymers with hydroxyl end groups (7).

On the hydrolysis of dichlorodimethylsilane with a large volume of water, the diol $(CH_3)_2Si(OH)_2$ has not been found, although there are indications of polymeric diols of the type $HO[(CH_3)_2SiO]xSi(CH_3)_2OH$ where x is large and which tend to condense by dehydration with the passage of time, thus forming still larger polymers.

Branched Chain Polymers

A combination of cohydrolysis of trichloromethylsilane and chlorotrimethylsilane followed by catalytic rearrangement of the product results in a compound of structure VI, which is isomeric with III when n equals two (7).

$$CH_3Si-[(CH_3)_3SiO]_3 \qquad VI$$

II. PROPERTIES

These cyclic and linear polymers have low boiling points compared to those of the saturated hydrocarbons of similar molecular weight. There is a small effect of temperature on viscosity, surface tension and fluidity.

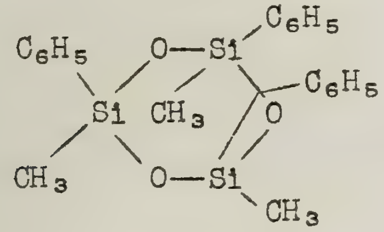
The trimethylsiloxy and ethoxy end blocked series, as well as that series with ethoxy groups in the chain, all have very similar properties. However, the cyclic polymers have greater viscosity as the size increases. The freezing points of the open chain polymers are much lower than the cyclic ones.

Physical properties such as density and refractive index vary only slightly as the molecular weight increases. Viscosity, on the other hand, increases progressively with small molecular weight increases.

Infrared data further substantiates the chemical evidence against the existence of the Si=O group since there is no absorption band due to this group (15). Also the absorption bands involving the Si-O bond have great intensity which is evidence of a large ionic character (11).

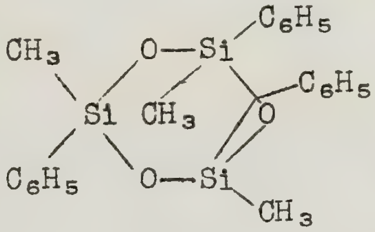
III. OPTICAL ISOMERISM

Cyclic siloxane polymers may become of interest ot the chemist as a means of studying cyclic isomeric systems, since the preparation of isomeric cyclic hydrocarbon systems often demands special types of syntheses, but in organosiloxane preparations it is possible to obtain these stereoisomeric forms very readily. For example, Hunter and coworkers (17) and Lewis (16) have obtained the two isomers of 2,4,6-trimethyltriphenylcyclotrisiloxane (VII, VIII) from numerous mixtures of methylphenylsiloxane polymers by seeding. However, they have been able to obtain only one of the four isomers predicted for the tetramer.



VII

cis



VIII

trans

Many complex cyclosiloxame polymer systems are possible and according to Hunter, careful selection of groups which aid crystallization would make possible the demonstration of numerous types of cyclic isomers which would be considerably more difficult to obtain for cyclic hydrocarbon systems.

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THE VON BRAUN CYANOGEN BROMIDE REACTION

Reported by Robert C. Sentz November 11, 1949

Cyanogen bromide was prepared for the first time in 1827 by Sérullos (1) from Br_2 and moist $Hg(CN)_2$. The simple Organic Syntheses method (2) using Br_2 and NaCN is presently available. Cyanogen bromide is extremely toxic and trimerizes on standing (3). Its dissociation into $Br^{\ominus}$ and $CN^{\oplus}$ ions (4) in organic solvents provides the most important key to its behavior toward organic nitrogen compounds.

(1) $$BrCN \xrightarrow[\text{solv.}]{\text{org.}} \underset{\text{To Anode}}{Br^{\ominus}} + \underset{\text{To Cathode}}{CN^{\oplus}}$$

Primary and secondary amines react readily with BrCN to form alkyl cyanamides and guanidines according to the following scheme (5).

(2) $$BrCN \xrightarrow{CH_3NH_2} HBr + CH_3\overset{H}{N}C{\equiv}N \xrightarrow{CH_3NH_2} CH_3\overset{H}{N}\overset{NH}{\overset{\|}{C}}\underset{H}{N}CH_3$$

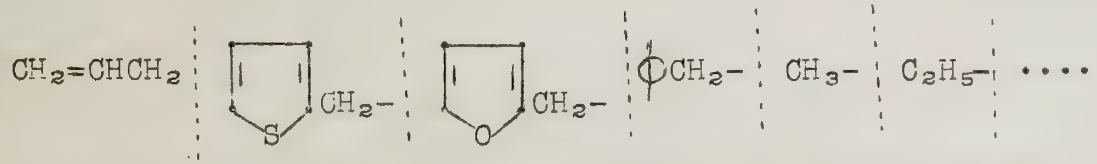
In 1900 J. von Braun first reported the more important reaction with tertiary amines which today bears his name (6).

(3) $$R''\overset{R'}{\underset{R'''}{N}}: \xrightarrow{BrCN} [R''\overset{R'}{\underset{R'''}{N}}C{\equiv}N^{\oplus}\ Br^{\ominus}] \longrightarrow \begin{cases} \xrightarrow{a} R''R'''NC{\equiv}N + R'Br \\ \xrightarrow{b} R'R'''NC{\equiv}N + R''Br \\ \xrightarrow{c} R'R''NC{\equiv}N + R'''Br \end{cases}$$

Variable amounts of quaternary side product are always formed if equimolar amounts of the tertiary amine and BrCN are mixed directly.

(4) $$R''\overset{R'}{\underset{R'''}{N}}: + R^xBr \rightarrow R''\overset{R'}{\underset{R'''}{N}}R^x]^{\oplus} Br^{\ominus}$$

Slow addition of the amine to an ether solution of BrCN prevents quaternization almost completely (7). From the study of acyclic tertiary amines the following series arranging R groups in their order of increasing resistance to displacement has been derived.

(5) 

increasing resistance to displacement →

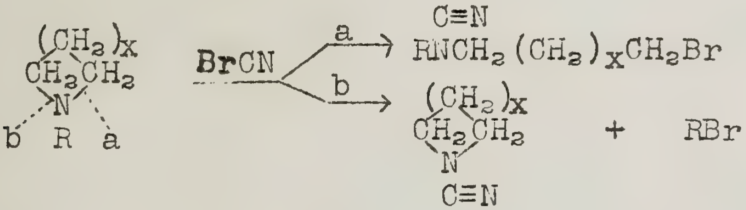
.... n-propyl ¦ i-propyl ¦ n-butyl ¦ i-butyl ¦ phenyl not displaced

increasing resistance to displacement →

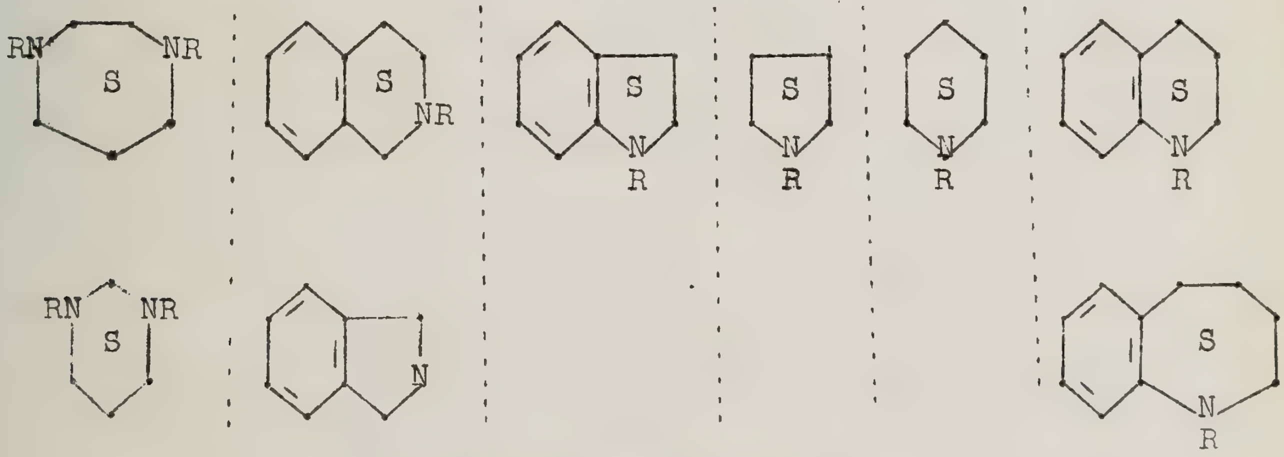
The increment in enhanced reactivity in the above series is variable but appreciable. In general the larger the size of adjacent groups the smaller the observed difference. Although supported by no published investigations the striking agreement of the above order with that anticipated from the assumption of cleavage by SN_2 attack of the $Br^{\ominus}$ upon an α-carbon of the quaternary nitrile X seems significant. For rules of thumb and more complete series of the above groups when bearing electron releasing and withdrawing substituents see reference 8.

If the tertiary nitrogen attacked by BrCN is part of an N-alkyl saturated ring system either ring opening and/or dealkylation may occur depending upon the character of R and the ring:

(6)



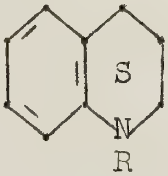
Investigation of the ease of cleavage of N-alkyl cyclic bases by v. Braun established this sequence of increasing stability (9).



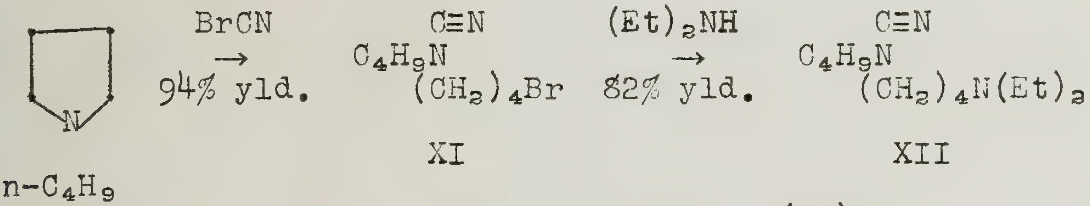
increasing stability to BrCN →

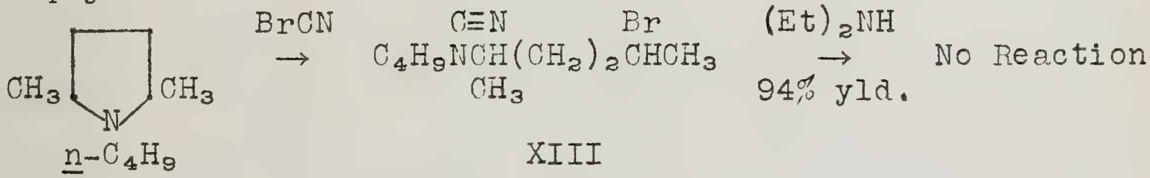
Data on the percentage of cleavage vs. dealkylation for different N-alkyl ring combinations which would allow correlation of the R and ring reactivity series given above are limited (10).

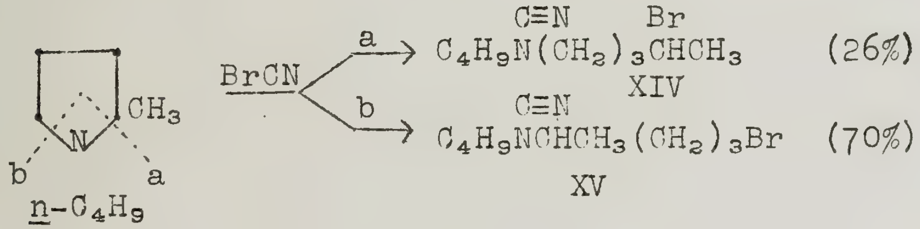
The few experimental results below provide examples of such interrelation.

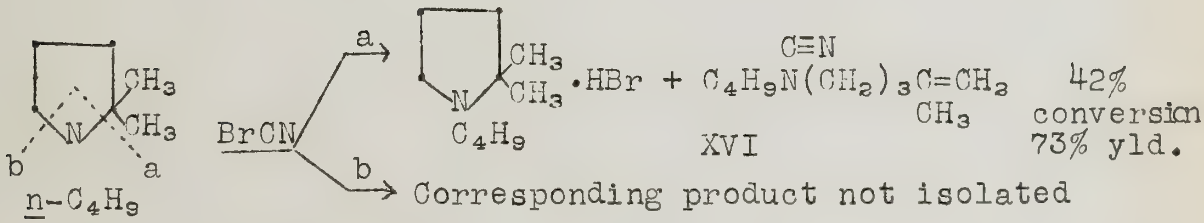
R	% Cleavage		% Dealkylation	% Cleavage		% Dealkylation
n-propyl	42		58	60		40
ethyl	20		80	33		67
methyl	--		100	--		--

Toward the investigation of the fate of ethylenimines and unsymmetrical pyrrolidines Elderfield and Hageman have recently synthesized compounds I to IX (8,11), treated them with BrCN, and identified the structure and percentage of products (8).

I 

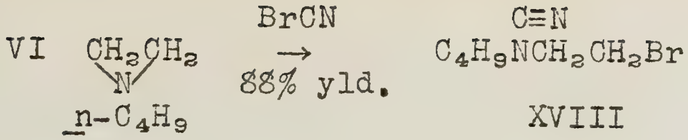
II 

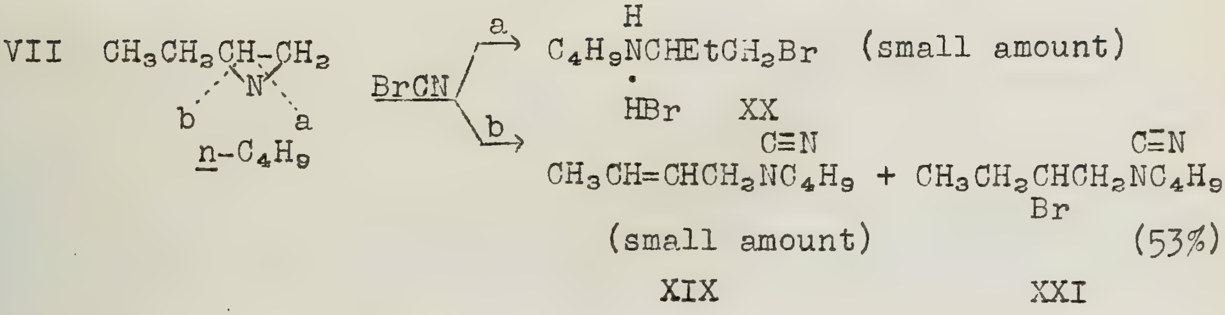
III 

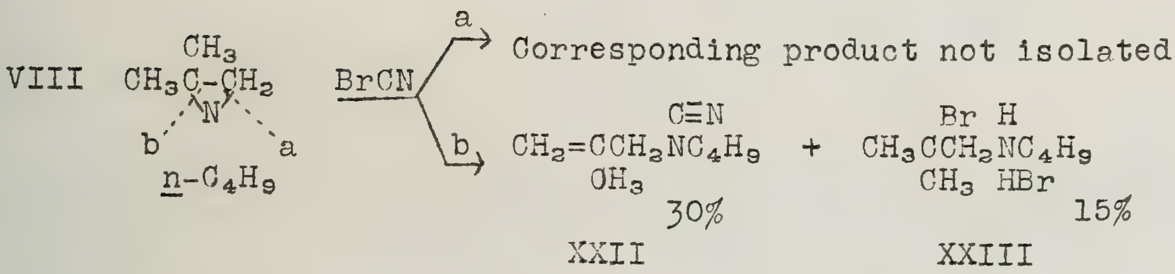
IV 

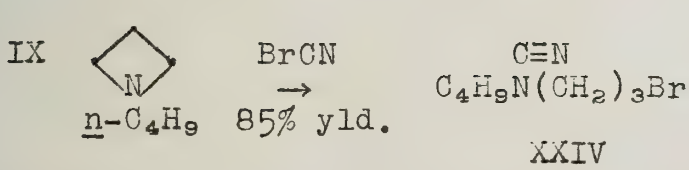
V CH_2CH_2 N Et $\xrightarrow[94\%\ yld.]{BrCN}$ $EtN(C{\equiv}N)CH_2CH_2Br$

XVII





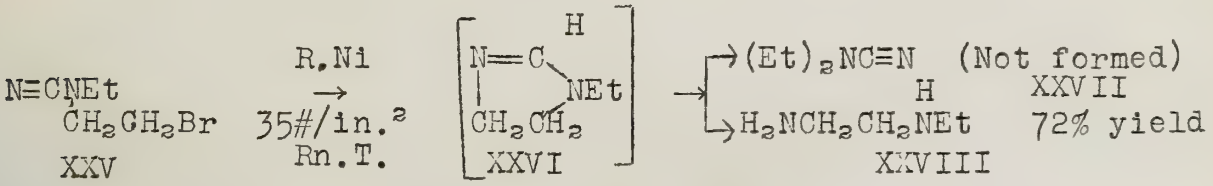




Insufficient compounds have been studied to justify any broad generalizations, but the authors conclusions in summary are: (1) No butyl bromide was formed in any case. (2) Symmetrical pyrrolidines I and II yield the expected primary or secondary halides XI and XII with no olefin formation. (3) The unsymmetrical α alkyl pyrrolidine III opened in both directions but the primary halo cyanamide XV predominated. (4) In competition between cleavage of the primary and tertiary C to N linkages in IV only rupture of the latter occurred to yield the unsaturated cyanamide XVI. (5) Simple N-alkyl ethylenimines form excellent yields of β-halo cyanamides which are stable to vacuum distillation and transient treatment with aqueous acid and alkali. (6) The N-alkyl-2-ethyl ethylenimine VII produced a moderate yield of halocyanamide XXI as the major product plus small amounts of elimination XIX and HBr XX cleavage products. The unequivocal structure proof of XXI has not been completed. (7) With VIII only the olefin and HBr cleavage products XXII and XXIII formed by fission of the tertiary C to N bond were isolated. (8) The N-alkyl azetidine was converted to the γ-bromo cyanamide XXIV in good yield.

Interesting developments of a more practical nature resulting from Elderfield's investigation are: (1) Formation of the

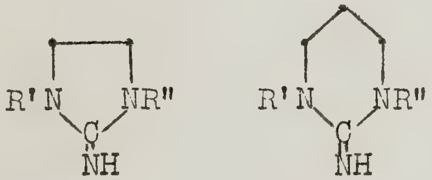
basic compound XXVIII rather than the expected halogen free diethylcyanamide XXVII from R.Ni reduction of ethyl-β-bromoethyl cyanamide XXV. The proposed intermediate XXVI was not isolated.



(2) The successful catalytic reduction of the δ-aminocyanamide XXIX to the diamine XXX in 38% conversion and 68% yield should be of interest in working with compounds sensitive to acid or alkali.

$$\underset{\text{XXIX}}{C_4H_9N(C{\equiv}N)(CH_2)_4N(Et)_2} \xrightarrow[\text{170°C.}]{\text{R.Ni, 1800\#/in.}^2} \underset{\text{XXX}}{C_4H_9NH(CH_2)_4N(Et)_2}$$

(3) The new type 5 and 6 membered cyclic quanidines XXXI and XXXII obtained in excellent yields from primary amines and the appropriate B or γ-halocyanamides are considered of interest as potential hypoglycemic agents by virtue of their relation to synthalin.



XXXI XXXII

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THE OPTICAL ACTIVITY OF DEUTERIUM COMPOUNDS

Reported by Roy H. Bible — November 18, 1949

The question of whether or not optical activity is possible in molecules in which the sole cause of asymmetry is the replacement of hydrogen by deuterium has intrigued numerous chemists during the last twenty years. The answer to this question has been sought by three principal methods: (1) attempted resolution of suitable deuterium compounds, (2) introduction of deuterium into an active compound in such a way that two groups become structurally identical but isotopically different, and (3) introduction of deuterium into a molecule already active so as to create a new asymmetric center (partial asymmetric synthesis). The hydrocarbons to be considered fall into two chief classes:

$$R(H)-\overset{*R'}{\underset{R''}{C}}-R(D) \ \text{I (e.g. } CH_3-\overset{C_2H_5}{CH}-CH_2D) \quad H-\overset{*R'}{\underset{R''}{C}}-D \ \text{II (e.g. } H-\overset{CH_3}{\underset{C_2H_5}{C}}-D)$$

Method (2) is an attempt to obtain the active forms of compounds of type I.

Tables I, II, and III summarize the unsuccessful efforts to prove the possibility of optical activity by methods (1), (2), and (3) respectively. Tables IV and V give some of the details of two recent successes.

It is interesting that many examples of a slight change in optical rotation resulting from the replacement of H by D in an optically active compound other than a hydrocarbon are known. Replacement of all the hydrogens on oxygen or nitrogen in the following active compounds, for example, causes a change in the rotation from the first to the second value given: mandelic acid, $[\alpha]_D^{20}$ $-173.27°\pm0.13°$ to $-179.10°\pm0.13°$ (16b), B-octanol $[\alpha]_{5461}^{25}$ 7.68° to 7.55° (21a), α-methyl benzylamine α_{5461}^{25} (10 cm) −45.39 to −43.77° (21b). There are cases in which no such change is detectable, however.

Table I - Unsuccessful Resolutions

(1) $C_6H_5CHDCHDCOOH$ (15)

(2) $C_6H_5CHDCOOH$ (21)

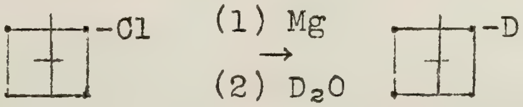
(3) $C_6H_5CH(C_6D_5)COOH$ (16a)

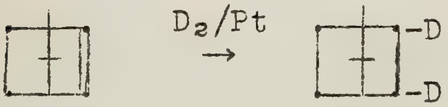
(4) $C_6H_5CH(C_6D_5)NH_2$ (7,1,9a)

(5) 

(9b)

Table II - Comparison of Groups Structurally Identical but Isotopically Different (All Inconclusive)

(1)  (4,17b,3,19)

(2)  (17b)

(3) $C_6H_5CH(CH_3)CH_2Br \xrightarrow[(2)\ D_2O]{(1)\ Mg} C_6H_5CH(CH_3)CH_2D$ (6,19)

(4) $C_2H_5CHOH\text{-}C{\equiv}CH \xrightarrow{D_2/Pt} C_2H_5CHOHCD_2CHD_2$ (18)

(5) $CH_3CH(C_2H_5)CH_2OH \xrightarrow{SOCl_2} CH_3CH(C_2H_5)CH_2Cl \xrightarrow[(2)\ DCl]{(1)\ Mg}$

$CH_3CH(C_2H_5)CH_2D$ (5,19)

Table III - Asymmetric Syntheses (All Unsuccessful)

(1) Maleic or fumaric ester $\xrightarrow[(2)\ (HOH)]{(1)\ D_2/Pt}$ same dideuterosuccinic acid (17a)

(2) CHO–CH(–O–)–CH₂–O– acetonide:

$$\begin{matrix} CHO & & \\ H\text{-}C\text{---}O & & CH_3 \\ | & C & \\ CH_2\text{-}O & & CH_3 \end{matrix} \xrightarrow{D_2/Ni} \begin{matrix} H\text{-}C\text{-}DOH & & \\ H\text{-}C\text{--}O & & CH_3 \\ | & C & \\ CH_2O & & CH_3 \end{matrix} \xrightarrow{HOH} \begin{matrix} HCDOH \\ | \\ H\text{-}C\text{-}OH \\ | \\ CH_2OH \end{matrix} \quad (14)$$

(3) $CH_2{=}CH\text{-}\underset{C_6H_5}{CHOH} \xrightarrow{D_2} CH_2D\text{-}CHD\underset{C_6H_5}{CHOH} \xrightarrow{[O]} CH_2D\text{-}CHD\text{-}\underset{C_6H_5}{CO}$ (10)

(4) $\alpha C_{10}H_7\text{-}C(C_6H_5){=}CH\text{-}\overset{C_6H_5}{\underset{C_6D_5}{C}}\text{-}OH$

or

$\alpha C_{10}H_7\text{-}\underset{OH}{C}(C_6H_5)\text{-}CH{=}\overset{C_6H_5}{\underset{C_6D_5}{C}}$

$\xrightarrow[\text{acid}]{\text{d-camphorsulfonic}}$

$$\begin{matrix} C_6H_5 & & C_6H_5 \\ & C{=}C{=}C & \\ \alpha C_{10}H_7 & & C_6D_5 \end{matrix}$$

(8)

Table IV - (Alexander and Pinkus) (2)

trans-2-menthene (diethylcarbitol) $[\alpha]_D^{25}$ 106.92° $\xrightarrow{H_2 + Ni}$ trans-menthane $[\alpha]_D^{25}$ 0.00±0.01°

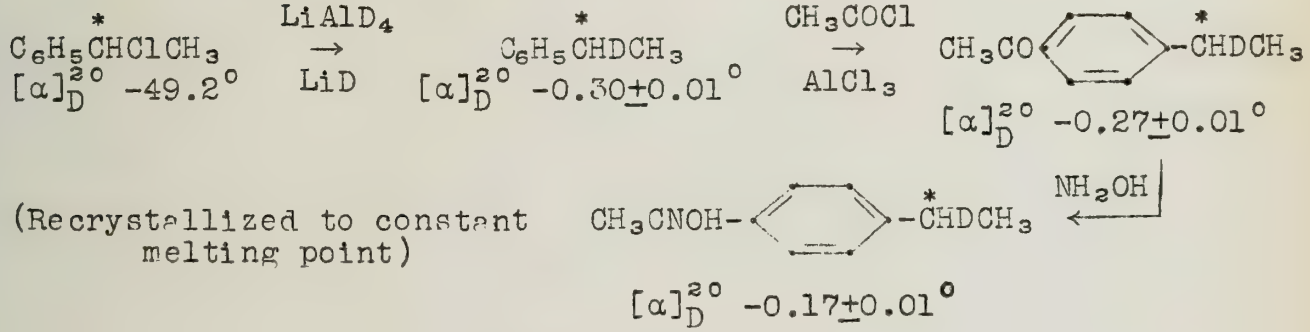
trans-2-menthene (diethylcarbitol) $[\alpha]_D^{25}$ 106.92° $\xrightarrow{D_2 + Ni}$ 2,3 dideutero-trans-menthane $[\alpha]_D^{25}$ -0.09±0.01°

No Change in Properties of Deutero Compound After:

I. a) Reduction with H_2
   b) Distillation over sodium

II. a) Treatment with alk. $KMnO_4$
    b) Nitric-sulfuric acid wash
    c) Distillation over sodium

Table V - (Eliel) (12)



(Recrystallized to constant melting point)

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RANEY NICKEL AS AN OXIDATION-REDUCTION CATALYST

Reported by Donald P. Hallada November 18, 1949

The role of Raney nickel as an oxidation-reduction catalyst is relatively obscure, although several examples appear in the literature. Paul (2) and Palfrey (3) have shown that certain alcohols can be dehydrogenated in the presence of Raney nickel to the corresponding aldehydes and ketones. The temperatures were high, and the yields low.

The action of Raney nickel as an oxidation-reduction catalyst may be explained in a similar manner to the action of palladium which serves, for example, as catalyst for reduction with hydrogen of naphthalene to tetralin or as a dehydrogenating agent for tetralin to naphthalene. The conditions for using Raney nickel would necessarily be more vigorous.

If an alcohol is heated with Raney nickel, dehydrogenation should occur until the equilibrium mixture is reached. Debois (4) heated 2-heptyl alcohol with Raney nickel for eight hours at 110-120° and thus obtained a 56% yield of 2-heptanone.

$$CH_3CHOHC_5H_{11} \rightleftarrows CH_3COC_5H_{11} + H_2$$

The yield could be raised to 88% by continuous distillation from the reaction mixture.

Debois also heated a mixture of isopropyl alcohol and 2-heptanone for 28 hours at 60-70° in the presence of Raney nickel. A 28% yield of acetone and a 34% yield of 2-heptanol were obtained.

$$CH_3CHOHCH_3 + CH_3COC_5H_{11} \rightleftarrows CH_3COCH_3 + CH_3CHOHC_5H_{11}$$

The latter reaction suggests the use of a hydrogen acceptor or donor to displace the equilibrium in oxidations or reductions, to obtain better yields.

Using cyclohexanone as the hydrogen acceptor, oxidation of a number of compounds was carried out (5,6), the results being tabulated below.

Table I

Cpd. Oxidized	Catalyst g./g. Cpd	Hours Reflux	Product isolated	% Yield
Cholesterol	2.0	24	Cholestenone	80
Benzoin	2.0	24	Benzil	35
Benzhydrol	2.0	22	Benzophenone	30
Dihydrocholesterol	2.5	24	Cholestanone	80
Epicoprostanol	1.5	24	Coprostanone	50
Fluorenol	2.5	24	Fluorenone	76

Reductions with Raney nickel using a solvent potentially capable of acting as a hydrogen donor are tabulated below (5).

Table II

Cpd. Reduced	Hydrogen Donor	Product isolated	% Yield
Cholestanone	Cyclohexanol	Dihydrocholesterol	50
Coprostanone	"	Epicoprostanol	20
Benzoin	"	Dibenzyl	58
Desoxybenzoin	"	"	20
Cholestenone	"	Dihydrocholesterol	10
Mesohydrobenzoin	"	Dibenzyl	17
Benzophenone	Diethylcarbinol	Diphenylmethane	75
"	Isopropanol	"	36
Desoxyanisoin	Cyclohexanol	p,p'-Dimethoxydibenzyl	80
Anisal-*p*-methoxyacetophenone	Diethylcarbinol	1,3-Di-*p*-methoxyphenylpropane	80
Stilbene	"	Dibenzyl	60
Benzilic acid	Isopropanol	Diphenylmethane	5
Laurone	"	Diundecylcarbinol	80
Ethyl *o*-benzoylbenzoate	"	*o*-Benzylbenzoic acid	86
Diphenylacetylene	Ethanol	Dibenzyl	77
Di-(4,4'-tetramethyldiaminobenzhydryl)	Isopropanol	4,4'-Tetramethyldiaminodiphenyl methane	50
3-Acetylquinoline	"	3-Ethyl-5,6,7,8-tetrahydroquinoline	62
9-Anthraldehyde	"	9-Hydroxymethylanthracene	10
		Anthracene	10

The types of reductions affected in this fashion were similar to those brought about by either high pressure hydrogenation (1), or by the action of alkali on nickel-aluminum alloy (7). Carbonyl groups, and activated ethylenic and acetylenic bonds in various environments were smoothly reduced. Hydrogenolysis of the carbon-oxygen bond occurred when it was α to an aromatic ring.

Reductions similar to those above have been attributed solely to the adsorbed hydrogen on the catalyst (8,9); however, the participation of a hydrogen donor solvent when present in such reductions has since been verified (5,10).

A reaction which probably belongs in the class of oxidations (dehydrogenations) by Raney nickel has been reported by Metayer (11). Heating certain formamides in the presence of Raney nickel resulted in the formation of moderate yields of aldehydes and ketones. The reaction may be formulated in general terms as follows:

$$R(R')CH\text{-}NHCHO \rightarrow R(R')CO \qquad R = H, \text{Aryl}, \text{Alkyl}$$

The structure of the amine fragment determines the final product in this reaction.

1. If the carbon attached to nitrogen is mono-substituted, the product is an aldehyde.
2. If the carbon attached to nitrogen is di-substituted, the product is a ketone.
3. If the carbon attached to nitrogen is tri-substituted, or if the nitrogen is part of a cyclic system, the amine is regenerated.

The reaction types are illustrated below.

1. $C_6H_5CH_2NHCHO \rightarrow C_6H_5CHO$

2. $C_6H_5CH(CH_3)NHCHO \rightarrow C_6H_5COCH_3$

3. $\begin{cases} C_6H_5NHCHO \rightarrow C_6H_5NH_2 \\ C_5H_{10}NCHO \rightarrow C_5H_{10}NH \end{cases}$

Yields are lowered by substitution of the nitrogen, but are improved by heating under pressure in an inert atmosphere. This reaction is not restricted to the formyl derivatives of amines. Both the acetyl and benzoyl derivatives of cyclohexylamine on heating in the presence of Raney nickel yielded cyclohexanone.

$$C_6H_{11}NHCOR \rightarrow C_6H_{10}O \qquad R = CH_3,\ C_6H_5$$

Metayer has suggested this reaction as a means of determining the degree of substitution of the carbon attached to nitrogen in an amine. The amine is converted to the formyl derivative, and heated with Raney nickel. As previously indicated, a monosubstituted amine is converted to an aldehyde, a di-substituted amine to a ketone, and either a tri-substituted amine, or an amine in which the nitrogen is cyclic result in regeneration of the amine.

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THE REACTIONS OF HYDROCARBONS WITH SULFUR

Reported by William W. West November 18, 1949

Introduction

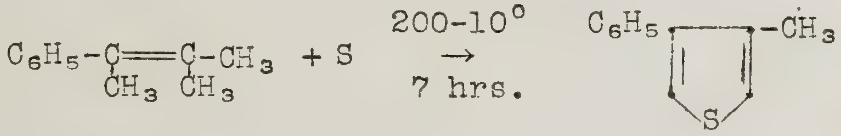
The high temperature reactions of sulfur with hydrocarbons, both saturated and unsaturated, have been considered by investigators as early as 1875. Present day interest in reactions of this nature has probably been due largely to the fairly recent (1947) announcement of a successful commercial preparation of thiophene (1).

The English workers, Farmer and Shipley (2), have done considerable work in the reactions of olefins and polyolefins with sulfur at 140°, especially with regard to rubber and polymer-like materials. Since their work has been partially covered in a previous seminar (3) it is merely necessary to mention their suggestion that sulfur acts by a free radical mechanism involving either the unsaturation electrons of the hydrocarbons or the active methylene groups.

Recent Preparative Work Involving Reactions of Sulfur with Hydrocarbons

A. Formation of substituted thiophenes.

The Russian workers Broun and Voronkov have used the reactions between sulfur and substituted styrenes to prepare a series of substituted phenyl thiophenes (4). No mention is made of a mechanism, except for the statement that the thiophene ring is formed by intramolecular ring closure through sulfur, with a diene intermediate. Examples of their products are:

(1) 

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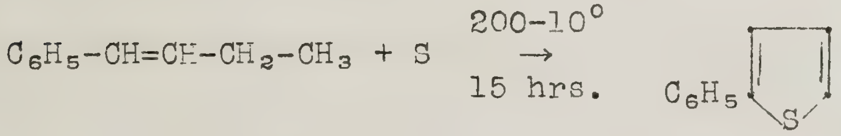
(2) 

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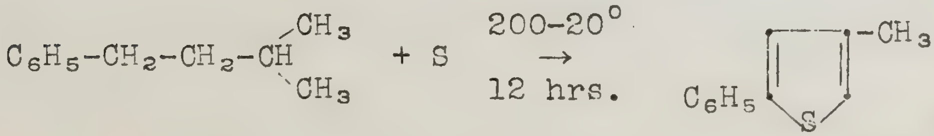
(3) 

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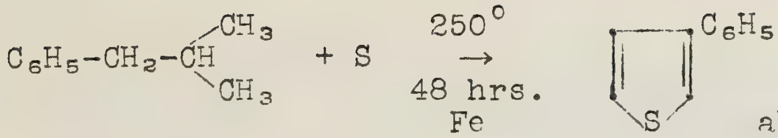
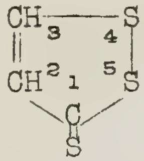
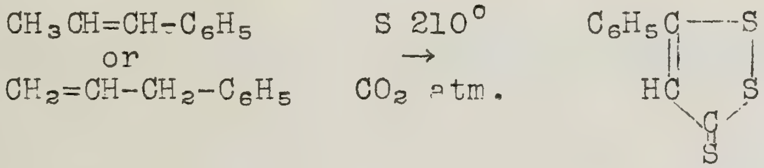
(4)  about 5%

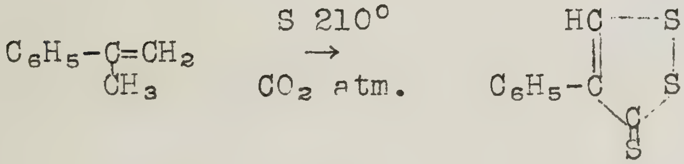
B. Formation of trithiones.

Recent work by Böttcher and Lüttringhaus (5) has produced a new type of heterocyclic ring which contains two sulfur atoms within the ring. These compounds are called trithiones and have the following structure and numbering system:



Generally, although not always, these colored solids are formed through the high temperature reactions of sulfur (in an atmosphere of carbon dioxide) with either substituted stryenes or substituted propenes which contain only three carbon atoms in the chain.

(1)  25%

(2)  30%

Isoprene forms a trithione of unknown structure, the emperical formula being $C_5H_6S_3$.

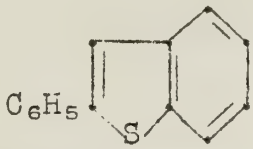
<u>A General Free Radical Mechanism for the reactions of Hydrocarbons with Sulfur</u>

The complex mixture formed from the reaction of sulfur with toluene at elevated temperatures has served as the experimental basis for the postulation by Horton (6) of a general free radical mechanism for the reaction of hydrocarbons with sulfur.

Earlier investigators have shown that:

$C_6H_5CH_3 + S \xrightarrow{\text{circa } 200^\circ}$ (a) $C_6H_5CH{=}CH{-}C_6H_5$,
(b) $C_6H_5CH_2CH_2C_6H_5$, (c) o-bitolyl,
(d) 1,2,3,4-tetraphenyl butane,
(e) tetraphenylthiophene
(f) compound $C_{14}H_{10}S$

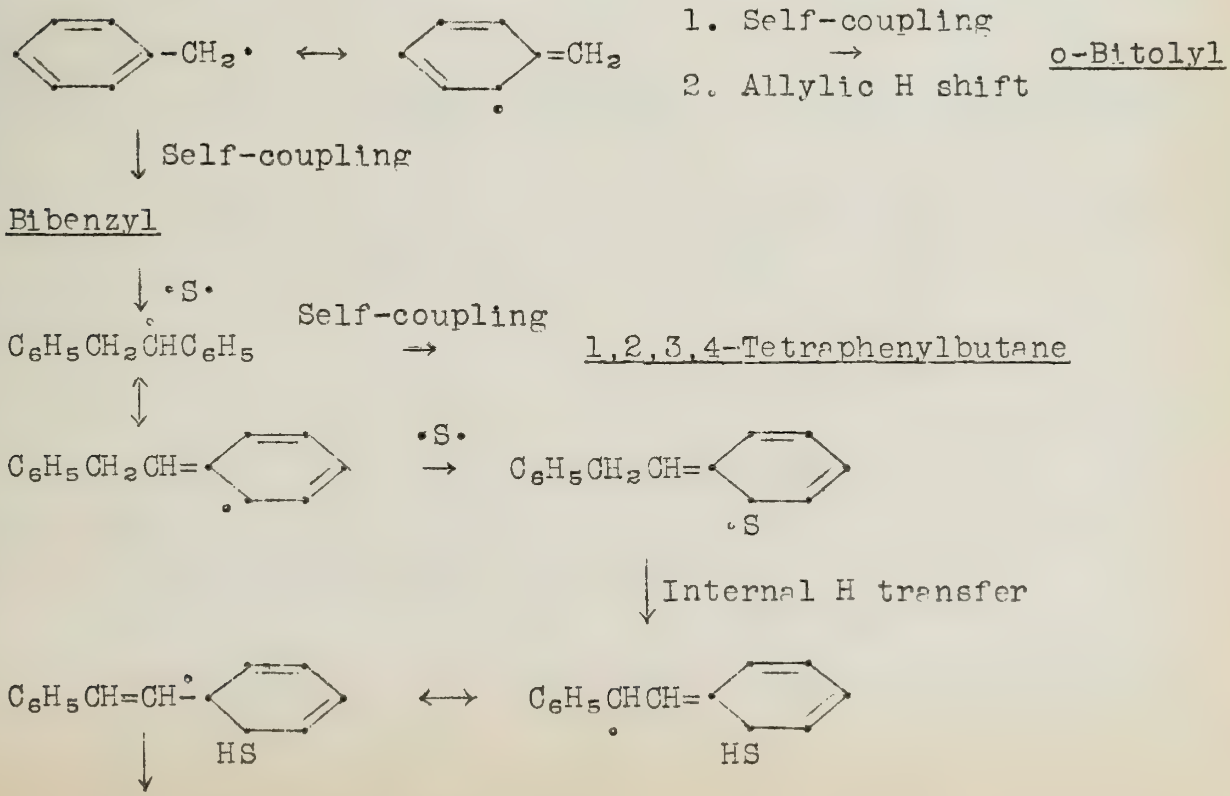
Realizing that characterization of compound (f) would be necessary in order to consider the mechanism involved, Horton was able to show that the compound was 2-phenylthianaphthene, through synthesis by standard procedures.

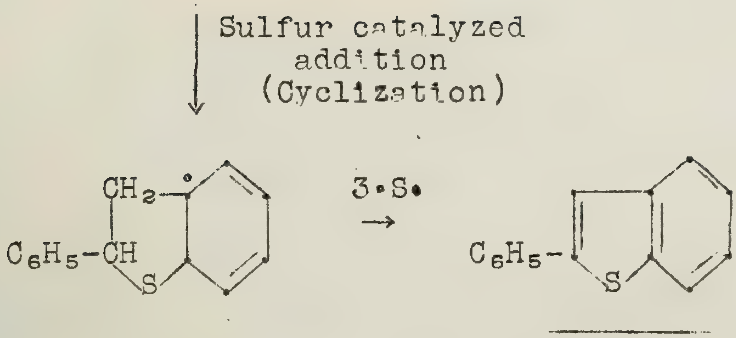


2-phenylthianaphthene

Having established the molecular products formed, Horton postulated a mechanism accounting for all known products. The products obtained, and the mechanisms involved, are shown below:

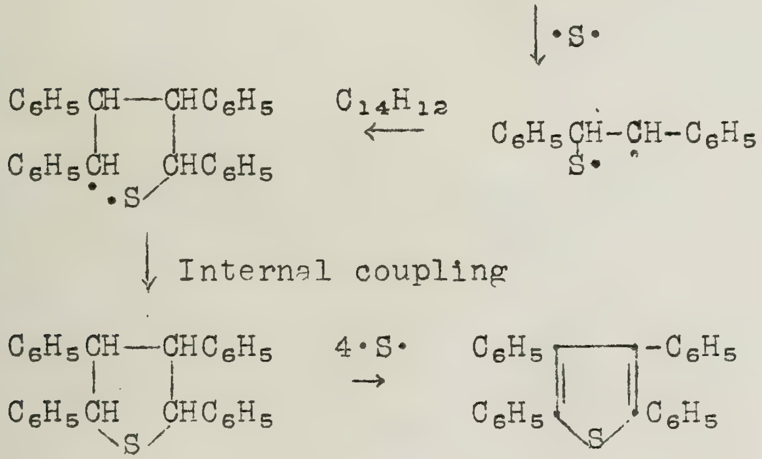
Reaction Products of Sulfur and Toluene
(actual products obtained are underlined)





2-phenylthianaphthene

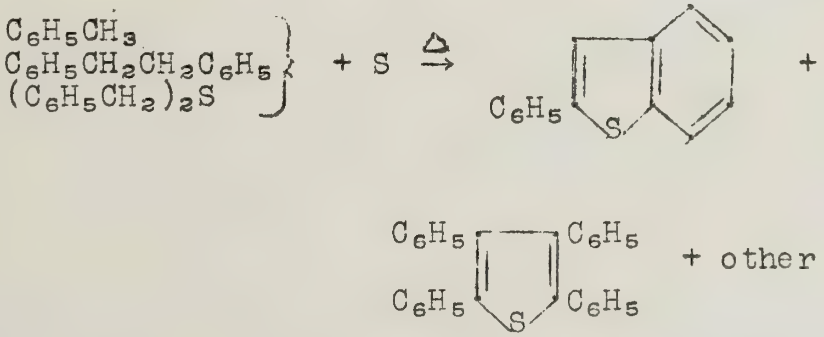
$$C_6H_5\dot{C}H_2CHC_6H_5 \xrightarrow{\cdot S \cdot} \text{Stilbene} \quad (C_{14}H_{12})$$



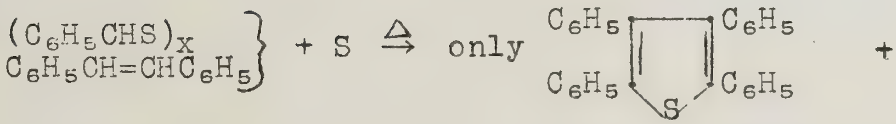
tetraphenylthiophene

A. Evidence in support of the free radical mechanism shown above:

(1) A benzyl grouping is necessary if 2-phenylthianaphthene is formed among the products.

(a) 

+ other products

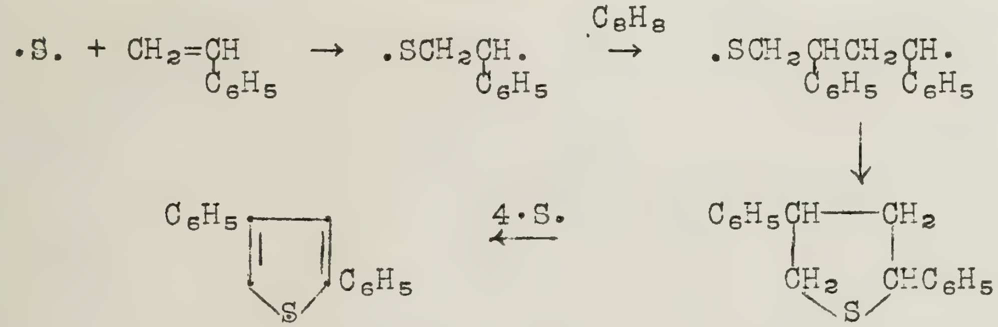
(b) 

other products

(2) Ortho position coupling favored by resonance hybrid forms of benzyl radical.
(3) Free radical nature of pyrolytic reactions such as pyrolysis of $(C_6H_5CH_2)_2S$ is supported by magnetic measurements which show that aryl disulfides form free radicals in large amounts by thermal dissociation (7).
(4) Sulfur is known to form molecular chains, $.(S_n).$, where n = 2 to 8.
    (a) .S. then acts as radical in various dehydrogenation steps.

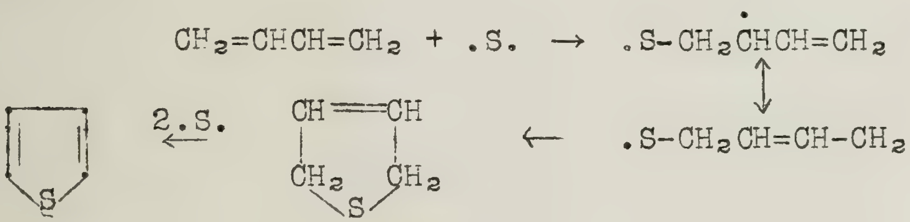
$$C_6H_5CH_3 + .S. \rightarrow C_6H_5CH_2. + H{:}S.$$

B. Ethylbenzene reacts with sulfur to form 2,4-diphenylthiophene, probably through an olefin intermediate, since styrene forms the same product (8). The following mechanism is postulated:

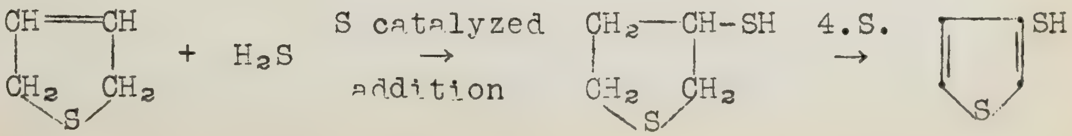


The "head to tail" mechanism is borne out by other work (9).

C. A similar mechanism is probably involved in the reaction of sulfur with conjugated dienes and the following sequence is suggested:



The formation of thiophene thiol, a by-product in the commerical preparation of thiophene, may be explained using the above intermediate:



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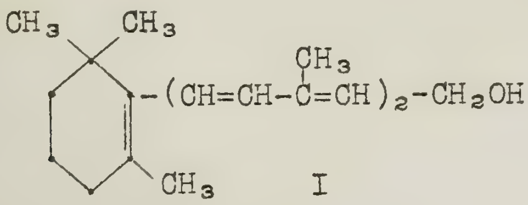
VITAMIN A AND SYNTHETIC ANALOGS

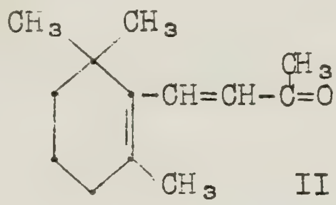
Reported by Henry C. Geller December 2, 1949

Vitamin A

The structure elucidation and early syntheses of Vitamin A (I) are well reviewed (1-3). Currently there are two synthetic approaches to the vitamin and its esters or ethers which give products of high biological activity in fairly good yields. β-Ionone (II) (4) is the starting material in both schemes.



I



II

Isler and his group have utilized the following synthetic schemes, $C_{13} \rightarrow C_{14} \rightarrow C_{20}$: (5,6) ($R_\beta$ = ring structure of I)

II $\xrightarrow{\text{Darzens Reaction}}$ R_β-CH_2-CH=C(CH_3)-CHO (III) + HC≡C-C(CH_3)=CH-CH_2OR (Grignard)

↓

R_β-CH_2-CH=C(CH_3)-CH(OH)-C≡C-C(CH_3)=CH-CH_2OR

↓ Partial H_2 (Preferential esterification when R=H)

R_β-CH_2-CH=C(CH_3)-CH(OH)-CH=CH-C(CH_3)=CH-CH_2OR'

↓ Allylic Rearr. (I_2 in pet.ether) and Dehydration

R_β-CH=CH-C(CH_3)=CH-CH=CH-C(CH_3)=CH-CH_2OR'

IV

Esters: R = H; R' = acetyl, butyryl, benzoyl, palmitoyl.
Ethers: R and R' = methyl, butyl, phenyl.

The overall yield from vitamin A acetate was 72%. All these compounds, especially the methyl and acetyl derivatives, show biological activity. Milas has established several routes to these same compounds along very similar lines (7). However, he considers

the product of the Darzens reaction to be a β,γ unsaturated C_{14} aldehyde (cf. III) (8).

Van Dorp and Arens have established the following route: $C_{13} \rightarrow C_{17} \rightarrow C_{18} \rightarrow C_{20}$ (9,10).

II $\xrightarrow[\text{Zn}]{BrCH_2CH=CHCO_2CH_3}$ $\xrightarrow{-H_2O}$ $\xrightarrow{\text{Sapon.}}$ $R_\beta-CH=CH-\overset{CH_3}{C}=CH-CH=CH-CO_2H$

$\downarrow CH_3Li$

$\downarrow H_2O$

$C_{19}H_{27}-CHO$ Vit. A Aldehyde $\xleftarrow{\text{Ethoxy-acetylene method}}$ $R_\beta-CH=CH-\overset{CH_3}{C}=CH-CH=CH-\overset{CH_3}{C}=O$

V

Meerwein Pondorff $\downarrow$ Later (11) LiAlH $\qquad$ $\downarrow$ $BrCH_2-CO_2R$, Zn, etc. $\downarrow$

I $\xleftarrow{\text{LiAlH}}$ $R_\beta-CH=CH-\overset{CH_3}{C}=CH-CH=CH-\overset{CH_3}{C}=CH-\overset{O}{\overset{\|}{C}}-OH$ (R)

VI

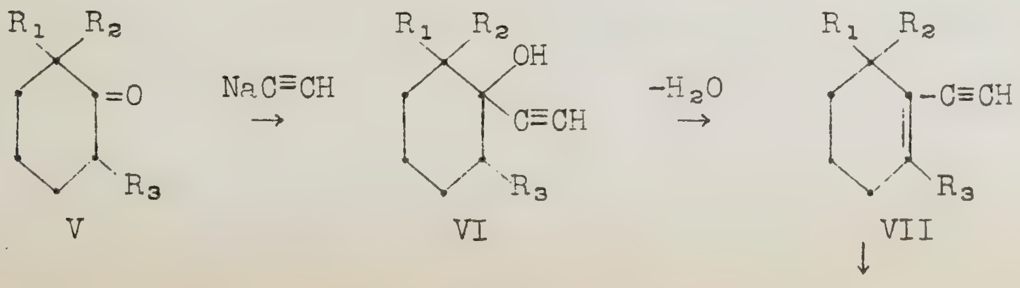
Schwartzkopf, et al. have improved the foregoing method by introducing a smooth reduction of Vitamin A acid or esters (VI) with the use of $LiAlH_4$ (12). Milas had also suggested this step (13).

Cawley, Robeson, et al. have announced without giving any details a new and different synthesis of Vitamin A (14).

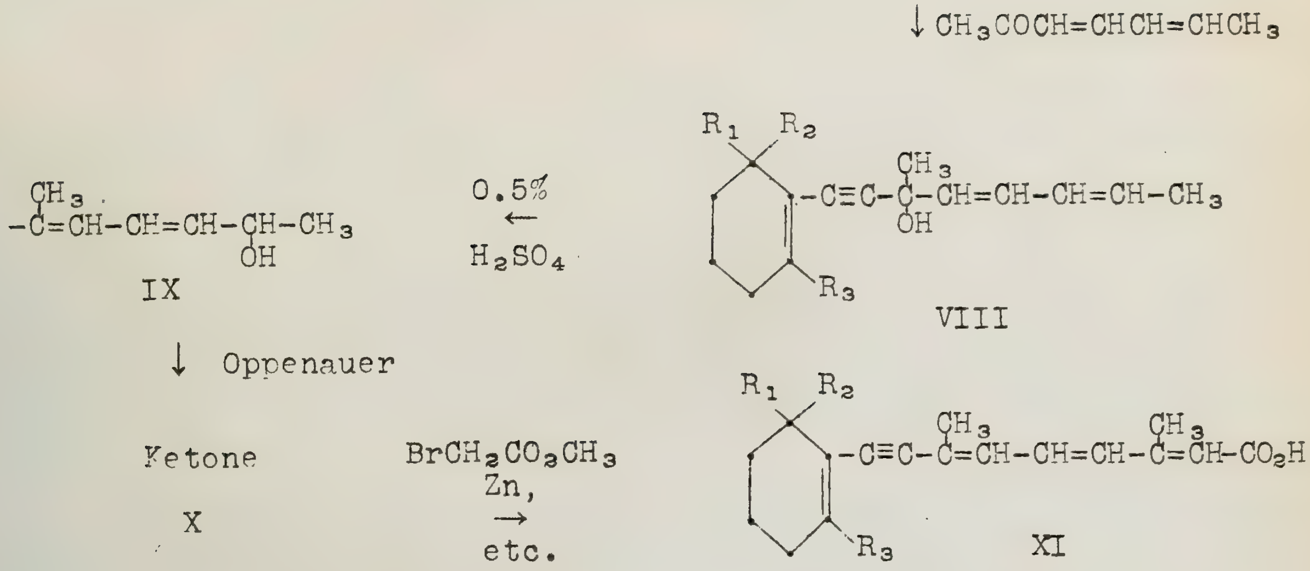
Analogs

Three groups have independently established a new route to a type of vitamin A analog (e.g., with various methyl groups removed), which will offer opportunities to study the relationship between molecular structure and biological activity and which may ultimately yield a total synthesis of the vitamin itself (15,16,17).

With cyclohexanol or its methyl analogs as a starting material, Heilbron, et al. have synthesized acid analogs of vitamin A.

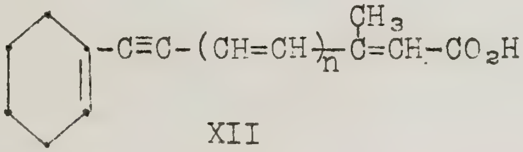


V VI VII



Cyclohexanol (V, $R_1=R_2=R_3=H$) condensed with sodium acetylide to give an ethynylcyclohexanol (VI) which, on dehydration, yielded an ethynylcyclohexene (VII). The Grignard reagent of VII was condensed with crotonylideneacetone to give the carbinol (VIII) which underwent anionotropic rearrangement. The ketone (X) was formed by an Oppenauer oxidation of the rearranged carbinol (XI). A Reformatsky reaction on the ketone (X) with subsequent dehydration and hydrolysis yielded a crystalline C_{17} acid (XI, $R_1=R_2=R_3=H$) in 20% overall yield. The sodium salt of this acid exhibits definite although weak physiological activity (15).

Variations on this new method are - (a) Use of methylcyclohexanones: Heilbron has prepared the C_{19} (XI, $R_1=R_2=CH_3$, $R_3=H$) and C_{18} (XI, $R_1=R_2=H$, $R_3=CH_3$) acids from 2,2-dimethylcyclohexanone (V, $R_1=R_2=CH_3$, $R_3=H$) and 2-methylcyclohexanone (V, $R_1=R_2=H$, $R_3=CH_3$) respectively. The former showed the expected biological activity while the latter unexpectedly did not (18). (b) Use of different intermediates to vary position of methyl groups in the chain: By substituting crotonaldehyde and sorbaldehyde for crotonylideneacetone and starting with cyclohexanone, Heilbron obtained a C_{14} acid (XII, n=1) in 45% yield and a C_{16} acid (XII, n=2) in 12% yield (19).



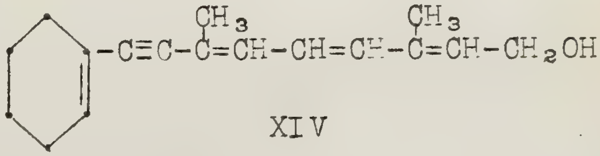
XII

The activity of the C_{14} acid was questionable, but the C_{16} acid was active. (c) Use of the anionotropic rearrangement to give the alcohol analog directly: 6-Methylocta-3,5,7-triene-2-one (XIII)

was synthesized (20) in order to be condensed with ethynylcyclohexene (VII) to give a tertiary carbinol which underwent rearrangement yielding a primary alcohol analog (XIV) of vitamin A (21).

```
    CH3          CH3
O=C-CH=CH-CH=C-CH=CH2
```

XIII



XIV

(d) Variation in the functional group by the newer methods mentioned earlier, e.g., reduction of the acids to primary alcohols with $LiAlH_4$ or conversion of the intermediate ketones to the corresponding analogs of vitamin A aldehyde by the ethoxyacetylene method of Van Dorp and Arens.

The critical step in this new synthesis, the dehydration of the ethynyl carbinol (VI), was smoothly accomplished at high temperatures with aluminum phosphate as a catalyst. Milas, in studying the synthesis of Vitamin A itself through this new route, has found that the dehydration of 1,6,6-trimethyl-1-ethynylcyclohexanol (VI, $R_1=R_2=R_3=CH_3$) by aluminum phosphate and other methods is difficult and gives small yields. Further work on the problem is in progress (16).

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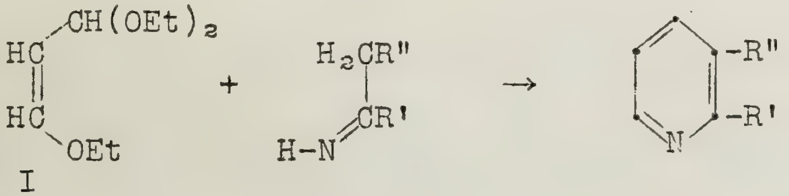
A SYNTHESIS OF SIMPLE HETEROCYCLIC COMPOUNDS

Reported by Roger W. Roeske December 2, 1949

Until 1939 there was no way of preparing pyridines substituted in the 2,3 positions only. Baumgartner and Dornow (1) demonstrated that the condensation of malonaldehyde with ketimine-enamine compounds of the type $HN{=}CR'{-}CH_2R'' \rightleftarrows H_2NCR'CHR''$ would give such compounds. This synthesis is analogous to those carried out by condensation of 1,3-ketoaldehydes and 1,3-diketones to obtain pyridines substituted in the 2,3,6 and 2,3,4,6-positions (2,3).

Malonaldehyde itself could not be used for the synthesis since it polymerized readily. β-Ethoxyacrolein diethyl acetal was successfully used in place of malonaldehyde.

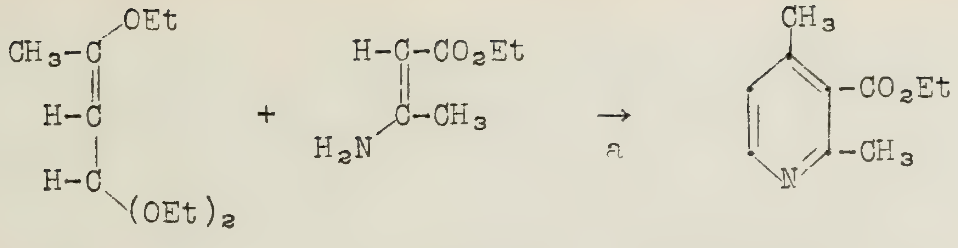


This synthesis is capable of wide application; R' and R" can be varied greatly, so long as R" is an activating group such as $-CO_2R$, $-CN$, and $-\overset{O}{\overset{\|}{C}}-CH_3$. Table I summarizes the results when the reactants were refluxed on a water bath for one to two days.

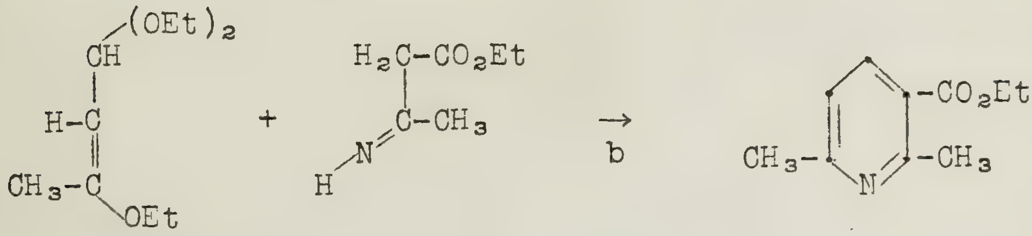
Table I

R'	R"	Product (pyridine derivative)	Yield
$-CH_3$	$-\overset{O}{\overset{\|}{C}}-OEt$	2-methyl-3-carbethoxy	30% (1) 98%(8)
$-CH_3$	$-CN$	2-methyl-3-cyano	43%
$-CH_3$	$-\overset{O}{\overset{\|}{C}}-CH_3$	2-methyl-3-aceto	25% (1) 90%(9)
$-CH_3$	$-\overset{O}{\overset{\|}{C}}-C_6H_5$	2-methyl-3-benzo	5%

The same product would be produced whether the enamine or the ketimine form reacted. However, if a derivative of β-ethoxyacrolein diethyl acetal were used, different products would result. To find which of the two reaction courses applied, β-ethoxycrotonaldehyde diethyl acetal and β-amino crotonic ester were mixed. If the reaction proceeded according to course a, the 2,4 dimethyl pyridine derivative should be formed; if according to course b, the 2,6 dimethyl derivative would result (4).



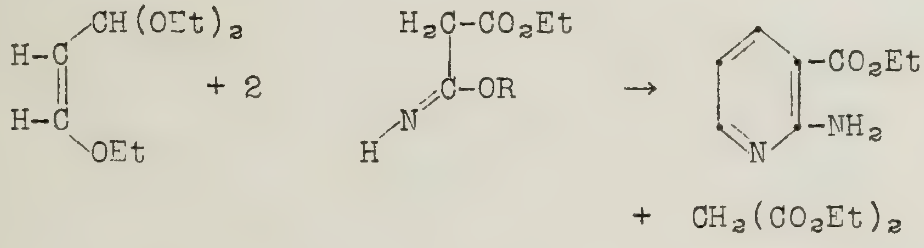
II III IV



Only the 2,6-dimethyl nicotinic ester could be isolated.

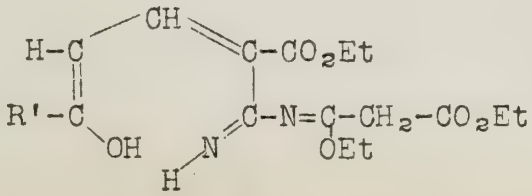
β-Ethoxycrotonaldehyde diethyl acetal was condensed with the nitrogen compounds mentioned in Table I to give analogous compounds having a methyl group in the 6-position.

It seemed plausible (5) that imino ethers which have an active methylene group would condense with aldehydes to give ethers. β-Ethoxyacrolein diethyl acetal was mixed with an imino ether derivative of malonic ester. The product was 2-amino nicotinic ester.



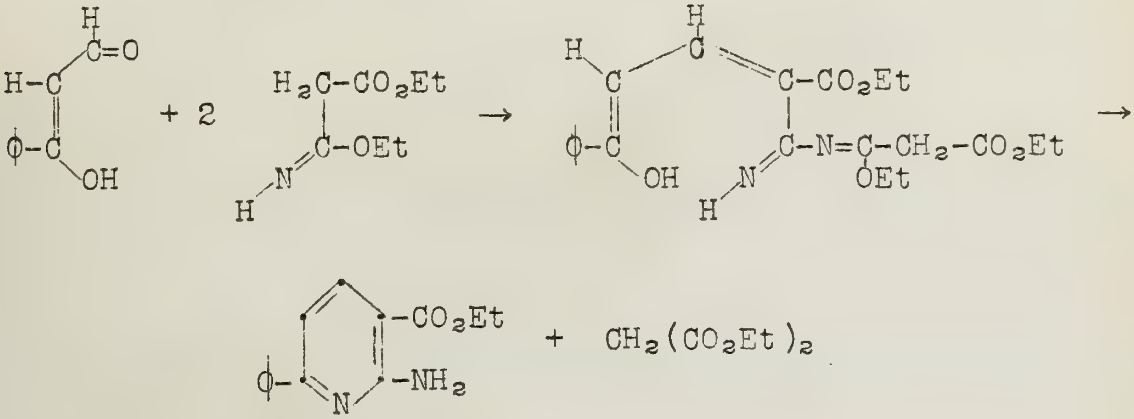
V

This unexpected reaction proceeds in this manner: first two molecules of imino ether combine with one molecule of dicarbonyl compound to form an intermediate VI which then, with ring closure and hydrolytic splitting out of malonic ester, forms 2-amino-pyridine derivatives.



VI

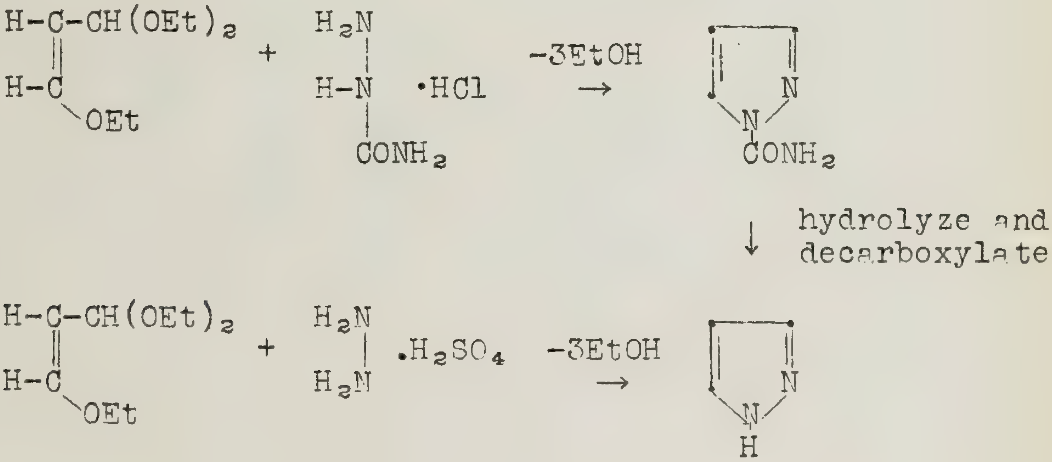
The intermediate VII in the reaction between benzoylacetaldehyde and the imino ether was isolated. After the intermediate was warmed in ethanol, 2-amino-6-phenyl nicotinic ester and malonic ester were isolated and identified.



VII

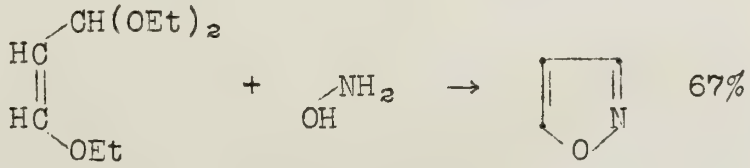
β-Ethoxyacrolein diethyl acetal was mixed with hydroxylamine, semicarbazide, and hydrazine, to determine whether simple aldehyde-type of condensation occurred or condensation to heterocyclic compounds (6).

The reaction of β-ethoxyacrolein diethyl acetal with semicarbazide hydrochloride gives an almost quantitative yield of the amide of pyrazole carboxylic acid.



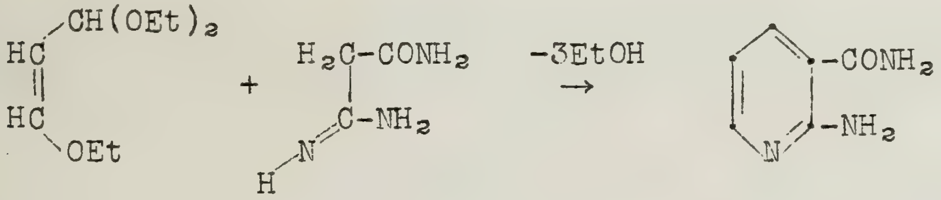
With hydrazine a 51% yield of pyrazole is obtained.

In an analogous reaction isoxazole resulted from the reaction between β-ethoxyacrolein diethyl acetal and hydroxylamine.



The only other preparation of isoxazole in the literature is that of Claisen (7), effected in 1903 by the reaction of propynal and hydroxylamine.

Condensation of β-ethoxyacrolein diethyl acetal with malonic acid amide-amidine gave a 25% yield of 2-amino nicotinamide.



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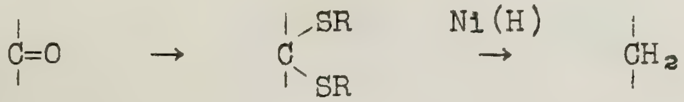
SOME NEW PREPARATIVE METHODS FOR ALDEHYDES

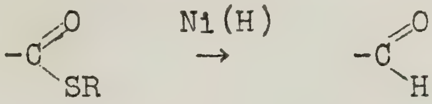
Reported by H. Sims December 2, 1949

The importance of aldehydes, both saturated and unsaturated ones, in the field of pharmaceuticals would seem to justify some attention to new or improved methods of preparing them.

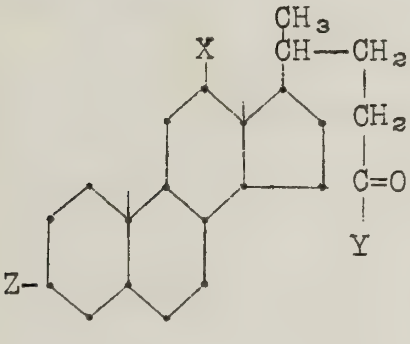
I. A new method has been developed for the preparation of steroid aldehydes related to the bile acids. This method evolved from the study by Bougault et al. in 1939-40 of the desulfurizing and reducing action of Raney nickel (5). Wolfrom and Karabinos utilized this property of Raney nickel to prepare 1- or 2-desoxy sugar alcohols from the corresponding mercaptals (10).



Later they extended this idea to thioesters, again replacing the -SR group with H which resulted in the formation of aldehydes. This represented a route from carboxyl to aldehyde that was an alternative to the Rosenmund method (11).



Extension and improvement of this method is reflected in the work of Levin et al. in 1947-8 on steroid acids (8). Partially deactivated Raney nickel was found to favor aldehyde rather than alcohol formation.



a. Y = -SEt

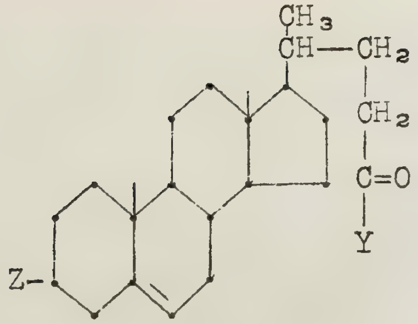
X = Z = -OC(=O)H (α)

b. Y = H

X = Z = -OC(=O)H (α)

I.

Ethyl 3α, 12α-diformoxythiocholanate (Ia) was converted to the corresponding aldehyde (Ib). Various cholenaldehydes (II) were also prepared from thio cholenates.



II

Ethyl, benzyl, phenyl or isopropyl thiocholenates were employed and gave yields ranging from 50-68%. The group on the 3-position could be hydroxy, formoxy, or acetoxy (in I or II) with little change in yield (9).

In general the advantages of this reduction are: (a) relatively simple procedures, (b) no reduction of nuclear double bonds, and (c) no hydrolysis of protective groups (some hydrolysis of the formoxy group).

II. A preparative method yielding α,β-unsaturated aldehydes has been developed in connection with work in the vitamin A series. Arens and van Dorp studied the anionotropic rearrangement of unsaturated tertiary carbinols and extended that reaction to alkoxy and aryloxy vinyl carbinols (1). The rearrangement products of the ethers were aldehydes, rather than alcohols as in the case of the vinyl carbinols. The following series of reactions were used for converting a ketone to an unsaturated aldehyde having 2 more carbon atoms.

$$CHBr_2CH(OEt)_2 \xrightarrow[EtOH]{Zn} BrCH{=}CHOEt \xrightarrow[\Delta]{KOH} HC{\equiv}C{-}OEt$$

$$RR'{>}C{=}O + BrMgC{\equiv}COEt \rightarrow RR'{>}\underset{OH}{C}{-}C{\equiv}C{-}OEt$$

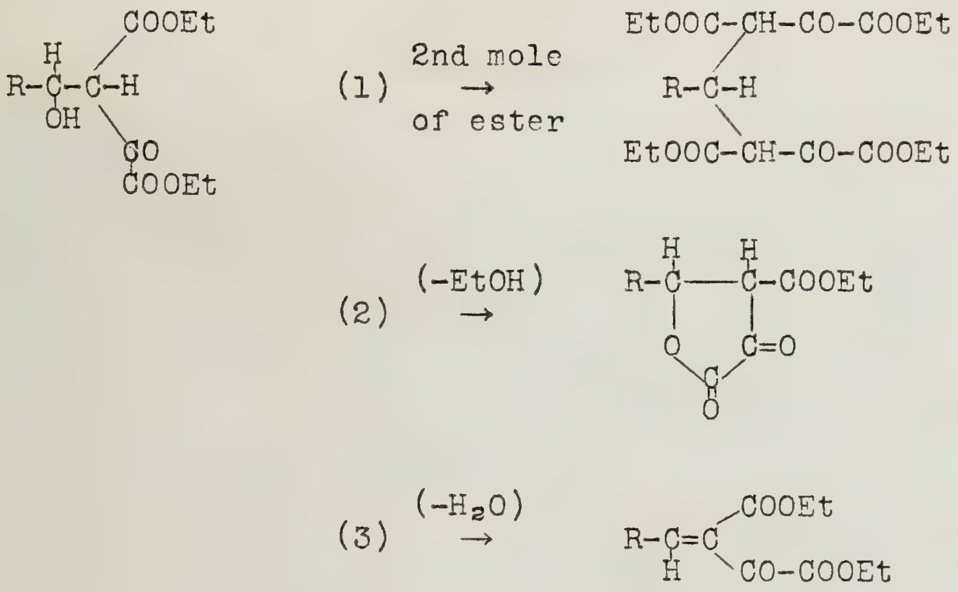
III. $\qquad H_2 \downarrow Pd{-}BaSO_4$

$$RR'{>}C{=}CH{-}CHO \xleftarrow[H^+]{dil.} RR'{>}\underset{OH}{C}{-}CH{=}CHOEt$$

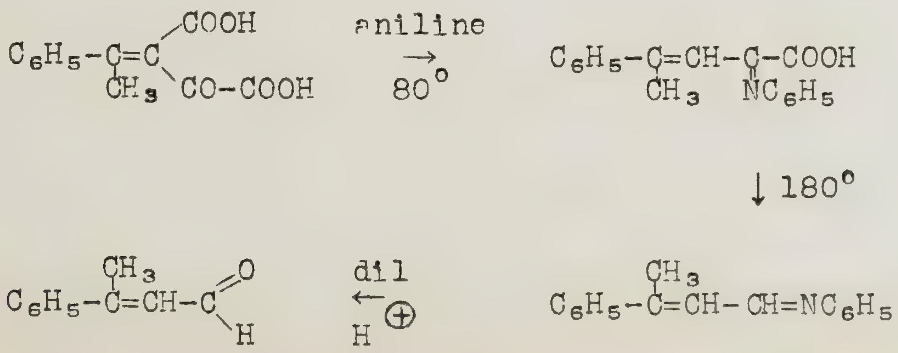
Vitamin A aldehyde was prepared from the related C_{18} ketone and β-ionone was converted to β-ionylidene acetaldehyde by the above method. Application of this method is not limited to the vitamin A series. Methyl heptenone and acetophenone were converted to citral and β-methyl cinnamaldehyde respectively.

Patent literature implies that a wide range of compounds may be used as starting materials (2,3). R and R' in compound III are described such that they may represent any ketone or aldehyde. They may also be linked to represent a cyclic ketone.

III. A second method for the preparation of α,β-unsaturated aldehydes was advanced by Arens and van Dorp (4). Studying the results of condensations of oxalacetic acid or its esters with aldehydes they came to the conclusion that the reaction could proceed by three paths after the initial molecule of oxalacetic ester had added to the aldehyde.



They found no reports of such condensations with ketones and were themselves unable to condense ketones with free oxalacetic acid. With the pyridine salt of hydroxymaleic anhydride (enol form of the anhydride of oxalacetic acid) a reaction occurred which was analogous to that indicated in path 3 above. Optimum conditions were worked out with acetophenone as the ketone.



The same series of reactions was carried out with β-ionone to yield β-ionylidene acetaldehyde.

More complicated technique and poor yields make this method less satisfactory than the preceding one for the preparation of α,β-unsaturated aldehydes.

IV. Lithium aluminum hydride reduction of amides and nitriles has been used to prepared amines (6). By using low temperatures (-70 to 0) and equivalent quantities of reactants, aldehydes have been prepared in excellent yields. Tertiary amides have proved to be most satisfactory in this method (7).

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THE STRUCTURE OF CITRININ

Reported by Bernard H. Braun December 9, 1949

Citrinin, $C_{13}H_{14}O_5$ (I), is an antibiotic isolated from several fungi of the genera Penicillium and Aspergillus (1-4) and also from a flowering plant, Crotalaria crispata (5). Discovered during a general survey of the products of fungal metabolism, a provisional structure, now known to be wrong (Ia), was advanced for it (6). Some inconclusive work on degradation products of citrinin was done several years later (7), but no further studies were undertaken till it was discovered the substance was an antibiotic (8,9,3). This led to methods of determining critinin (10,11) and to renewed structural studies, which showed (Ia) is incorrect (12,13) and eventually led to formula (I) (14-19).

The original work (1) showed citrinin is a levorotatory, monobasic acid, having one phenolic hydroxyl group and giving a positive iodoform test. Reduction gives a colorless dihydro compound, reoxidized easily by atmospheric oxygen, which has two phenolic hydroxyl groups. Degradation of citrinin was best accomplished by hot dilute sulfuric acid, which caused the following reaction: $C_{13}H_{14}O_5 + 2H_2O = CO_2 + HCO_2H + C_{11}H_{16}O_3$ with nearly quantitative yields. The $C_{11}H_{16}O_3$ fraction consisted of two compounds, about 90% "A" (levorotatory) and 10% "B" (optically inactive). "B" was regarded as racemate of "A" on inconclusive evidence and further work was confined to "A" (II).

"A" has two phenolic and one alcoholic hydroxyl group and its triacetate on hydrolysis yields "B"; its dimethyl ether with alkaline potassium permanganate yields a lactone $C_{13}H_{16}O_4$ (III) i.e. $C_{10}H_{10}(OCH_3)_2\left\langle\begin{matrix}O\\ |\\ CO\end{matrix}\right.$ in very poor yield. "A" itself on alkali fusion furnishes a phenol $C_9H_{12}O_2$ (IV) which from its reactions is a resorcinol derivative. The dimethyl ether of this phenol with alkaline potassium permanganate yields two acids (V) and (VI) in low yield; both of these are benzoic acids. All these compounds were unknown at the time.

An attempt was made (6) to derive a structure for citrinin from these facts. Misled by some color-reactions (IVa), (Va) and (VIa), respectively, were assumed for (IV), (V) and (VI); this leads to (IIa) for (II) and (Ia) for (I); a less likely possibility is (Ib). The lactone $C_{13}H_{16}O_4$ would be (IIIa).

Several years later (7) an attempt to synthesize all seven position isomers of (IV) with the two hydroxyls in meta-position led to the synthesis of four of them, among them (IVa), melting point 98-99°. (IV) from citrinin had melting point 97-99° (1), but on comparing the two it was found the natural product had deteriorated on standing and had melting point 65-70°; thus no mixed melting point could be taken and the identity of (IV) was left in doubt.

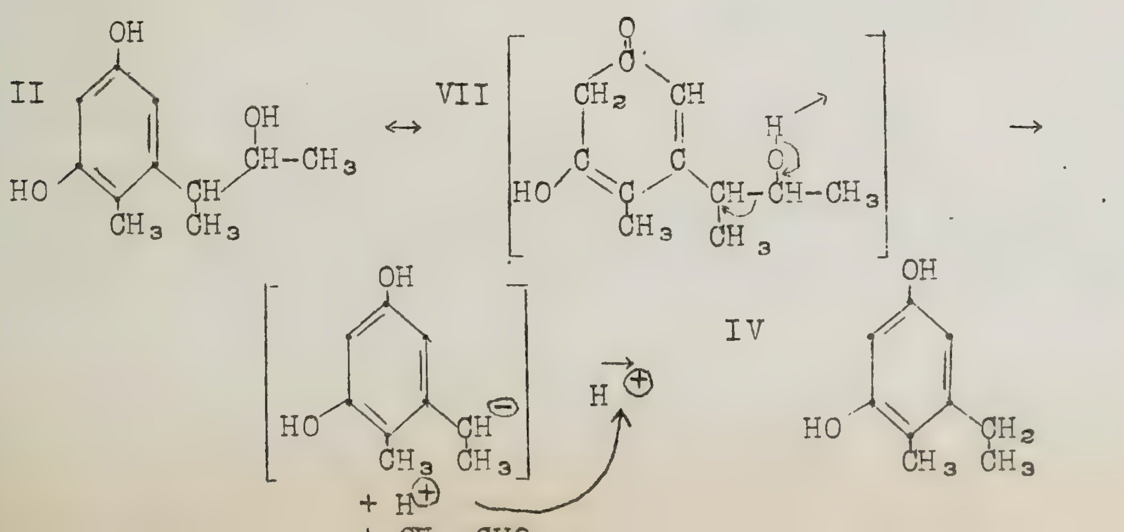
Criticism was made (12) of the reliance that had been placed on color reactions (7) and synthesis demonstrated that (Va) and (VIa) are different from natural (V) and (VI), thus making formulas (Ia), (IIa) and (IVa) untenable as well. At the same time it was concluded (13) that (Ia) and (IIa) were wrong, since (I) and (II) coupled with one respectively two molecules of diazonium salts, while these formulas predict respectively none and one molecule. These two groups of authors also prepared natural (IV) and found melting points 67-70°, respectively 68-69°, never obtaining the form melting point 97-99° of (1).

The next work published was a brief note (14) showing by synthesis that the correct structures were (IV), (V) and (VI) respectively ((IV) with melting point 67-69°) and showed how the previous authors (1) obtained (VI) in very impure condition (which may explain the misleading color-reactions). (I) and (II) have three C-methyl groups; this led to (II) being proposed as structural formula, while that of (I) was not considered.

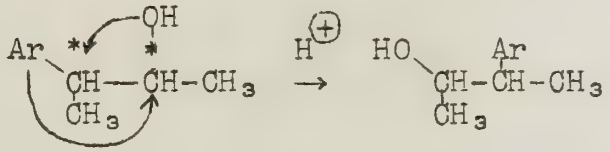
Another group of workers in a very brief note (15) claimed priority of synthesis of (IV) and stated the form with melting point 94-95° is anhydrous, the lower melting one hydrated. They also stated that undescribed work on citrinin, citrinin-methyl ether and other derivatives suggested (I) as the correct formula.

Meanwhile the Indian workers (16 cf. 13) also came to the structural formula (IV), basing their reasoning not on synthesis but on a study of the absorption spectra of the azo compounds from (IV) and from various known azo derivatives of substituted resorcinols. They came to the same conclusions as to the various melting points of (IV), and the purity of (VI) as the previous workers. Structure (Ic) was proposed for citrinin itself, and structure (II) was accepted (14).

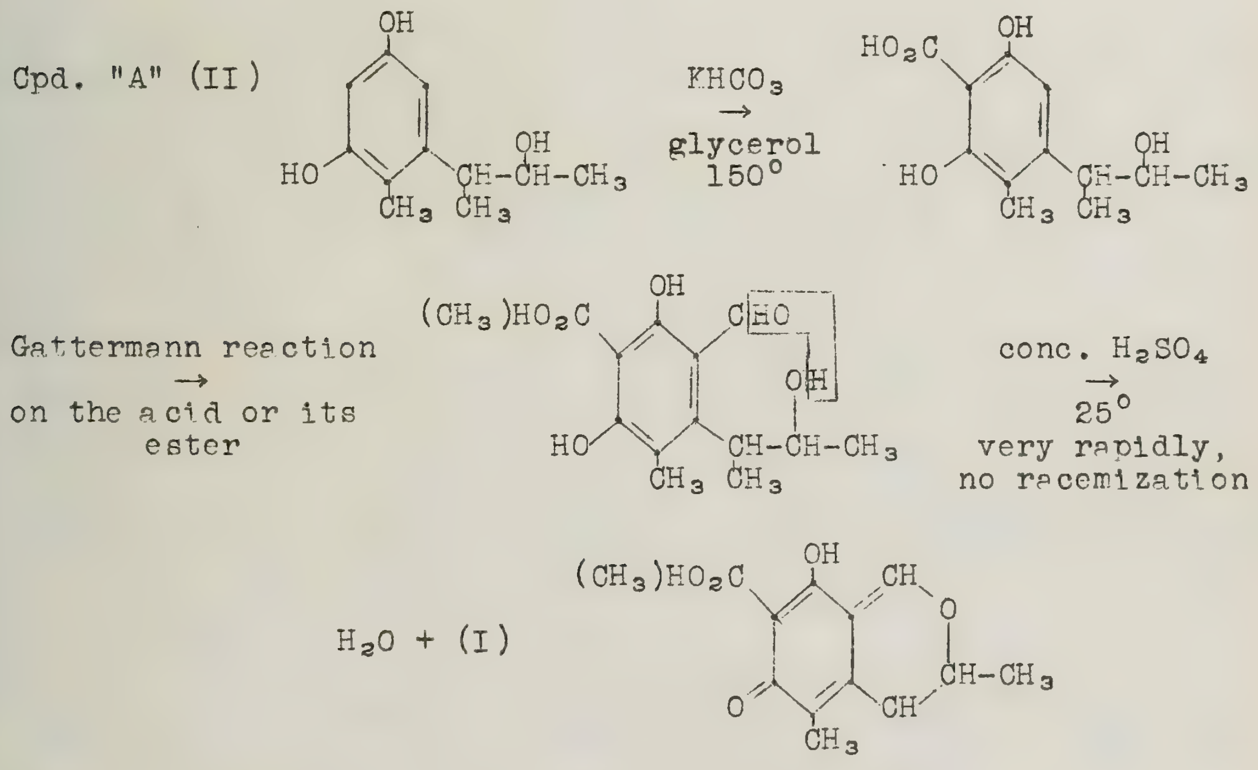
Cram next published a detailed article (16) which repeated previous work in full (14) and also proposed reaction mechanisms; he explains (II) alkali fusion → (IV) as a reverse aldol reaction on the tautomer (VII) which is a vinylog of a β-hydroxy ketone.



The lactone, $C_{13}H_{16}O_4$, is then (III); the racemization of "A" (II) to "B" is confirmed, and it is shown to occur only in acid, not in alkaline solution. Thus it is probably a Wagner-Meerwein rearrangement with migrating aryl group, which leads to a product structurally identical with the starting material, but with the two asymmetric carbon atoms inverted. Other possible structures for (II) are excluded by model substances. For citrinin itself, structure (Ic) is proposed, with (Id) and (Ie) as less likely alternatives.

II 

Recently other authors (15) in another extremely brief note (18) stated that natural and racemic citrinin of formula (I) has been synthesized as follows

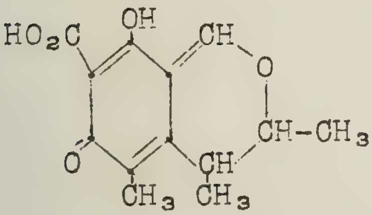


The same sequence from "B" leads to racemic (I).

The authors also state (no details given) that the dimethyl ether of "A" has been synthesized by way of the dimethyl ether of "B", but that demethylation yields "B". Thus the only step lacking in a total synthesis of l-citrinin is resolution of "B" (or one of the subsequent products).

The last article published (14) provides evidence for the structure of "A" and "B" (II) by showing "A" undergoes the Oppenauer oxidation to an optically active ketone and gives a

positive iodoform reaction. It is also proved that "B" is racemic "A" by direct racemization, and by resolving "B" triacetate to "A" triacetate and its antipode. The authors propose, evidently in ignorance of previous work (18), (Ic) or less, probably (I) for citrinin.



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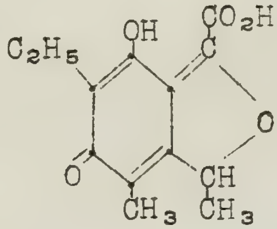
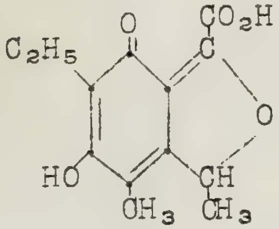
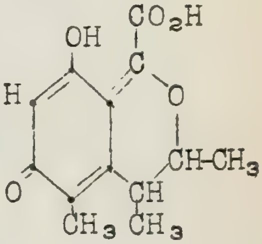


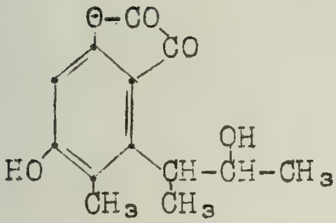
Ia



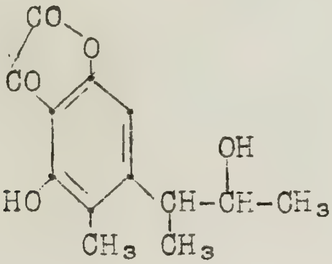
Ib



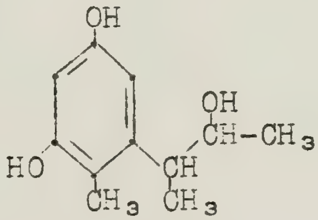
Ic



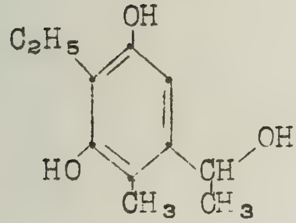
Id



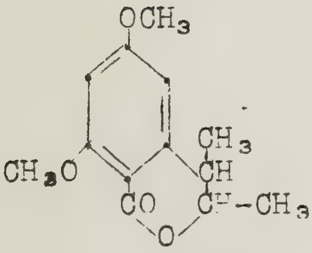
Ie



II



IIa



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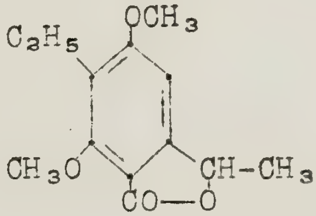
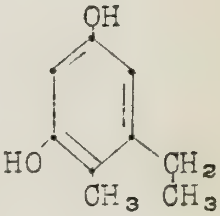
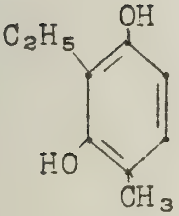


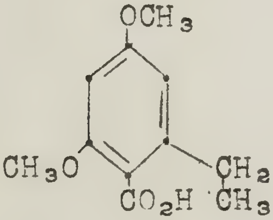
IIIa



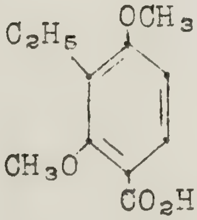
IV



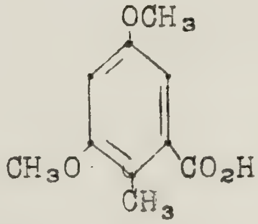
IVa



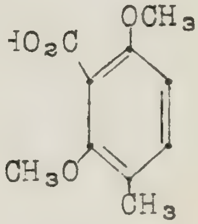
V



Va



VI



VIa

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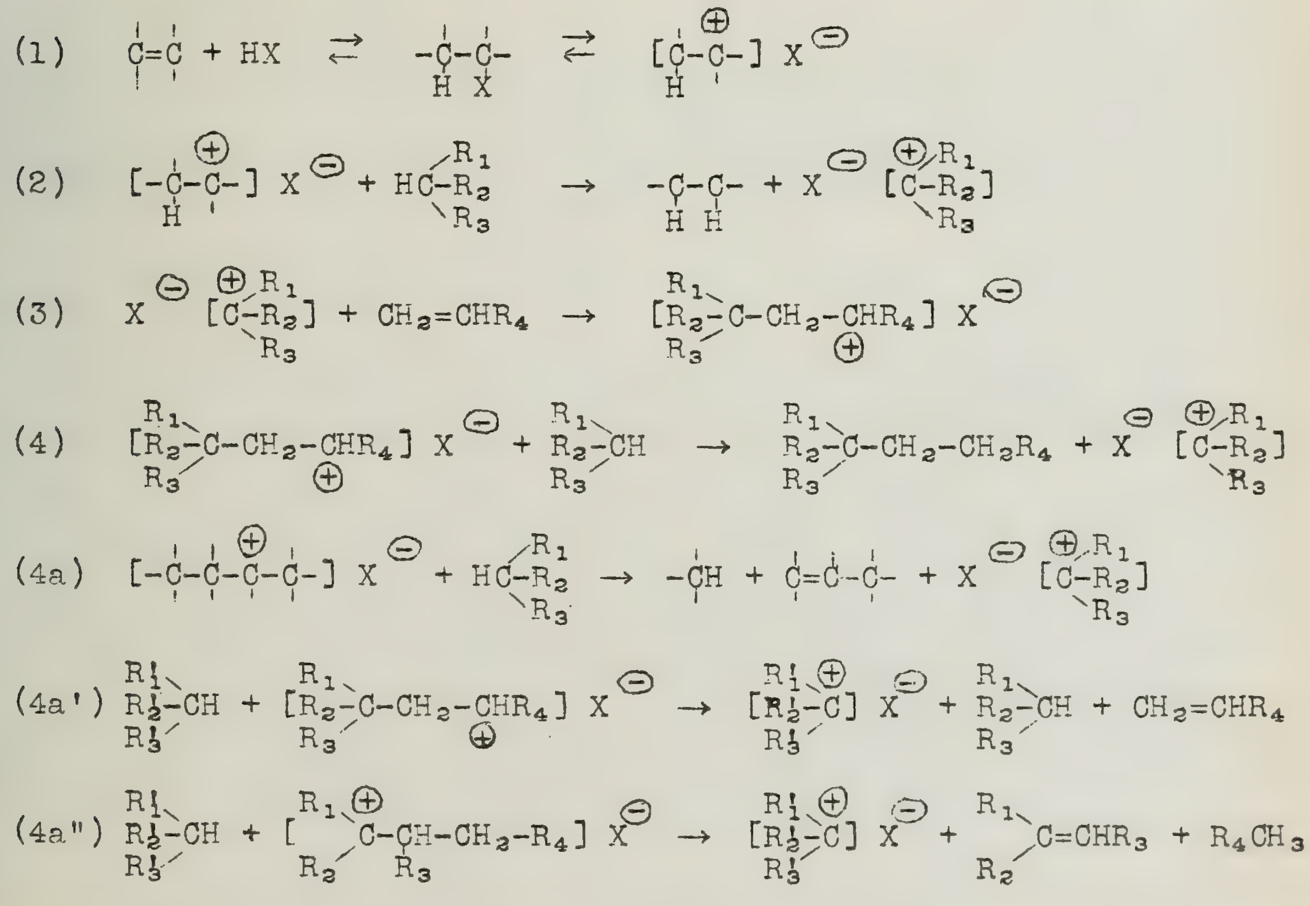
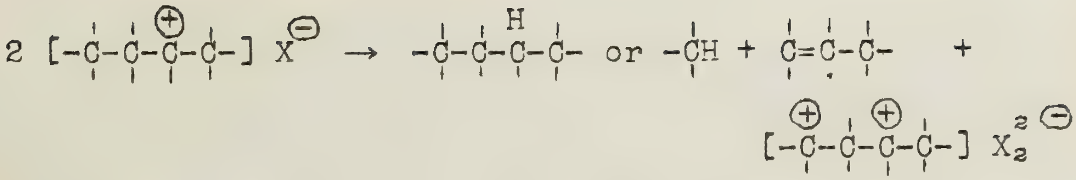
THE MECHANISM OF THE CATALYTIC ALKYLATION OF ISOPARAFFINS WITH OLEFINS

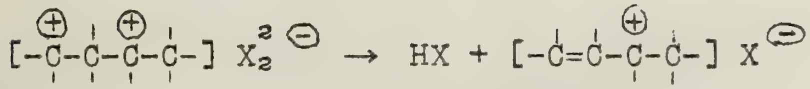
Reported by J. A. Fuller December 9, 1949

Because of its importance in synthesizing high octane fuels this reaction has been widely investigated. Reaction mechanisms proposed by Ipatieff and Grosse (1), Birch (2,3) and McAllister (4) are concerned essentially with carbon-carbon and carbon-hydrogen bond cleavage in the isoparaffin followed by addition to the olefin. These schemes do not account for the structures of many of the products isolated. Schmerling's theory (5), involving carbonium ion intermediates, is well founded and more widely accepted at present.

Caviët, van Steenis and Waterman (6,7) have suggested a mechanism which is an enlargement on Schmerling's theory. The purpose is to explain the formation of "B" oil (a highly unsaturated, polymeric hydrocarbon-catalyst complex formed in all such alkylations), disproportionation and the structure of the main products.



(5) 

(6) 

To account for the reactions possible in this type alkylation the reaction conditions are divided into four extreme cases:

I. Intimate catalyst contact with isoparaffins (HF or H_2SO_4 emulsified with hydrocarbon)
   (a) Olefin used polymerizes relatively slowly (1-butene).
   (b) Olefin used polymerizes relatively rapidly (isobutene).

II. Poor catalyst contact with isoparaffin or small active catalyst concentration (Solid or slightly soluble catalysts).
   (a) Same as I(a).
   (b) Same as I(b).

Case I (a) - Reactions (1) through (4) will predominate. The main product is the hydrocarbon corresponding to the most stable form of the carbonium ion on the left side of equation (4). Hardly any "B" oil is formed and no higher hydrocarbons. Disproportionation may occur to a small extent by:

(a) The carbonium ion formed in (2) may lose a proton to form a new olefin.

(b) The carbonium ion formed in (3) may disproportionate to give starting materials (equation (4a')) or may rearrange and then break down to give two new hydrocarbons (reaction (4a")).

Case I (b) - Reactions (1), (2) and (3) take place as in I(a). Reaction (4) is suppressed because of the reactivity of the olefin and larger carbonium ions are formed in (3). These polymer carbonium ions are converted to hydrocarbons mainly by reaction (4a) (ref. 8). Isomerization here may give rise to products which do not correspond to alkylate or starting material in the number of carbon atoms. More "B" oil forms than in I(a) because the polymer carbonium ions may act as hydrogen donor (reaction (5)). The double carbonium ion formed then loses a proton (reaction (6)). This unsaturated carbonium ion may re-enter the cycle which eventually results in a series of conjugated double bonds.

Case II (a) - Reaction (3) will again yield polymer carbonium ions and a short reaction time will produce only polymers and unchanged starting materials. After a long reaction time alkylate will be

formed by reaction (4) but (5) and (6) also occur and more "B" oil is obtained than in cases I(a) or I(b). Loss of a proton from polymer carbonium ions gives rise to partly unsaturated, high molecular weight hydrocarbons.

Case II (b) - After a short reaction time almost all the olefin will be recovered as polymer. Increasing the reaction time results in formation of some alkylate but mostly "B" oil and higher, partly saturated hydrocarbons.

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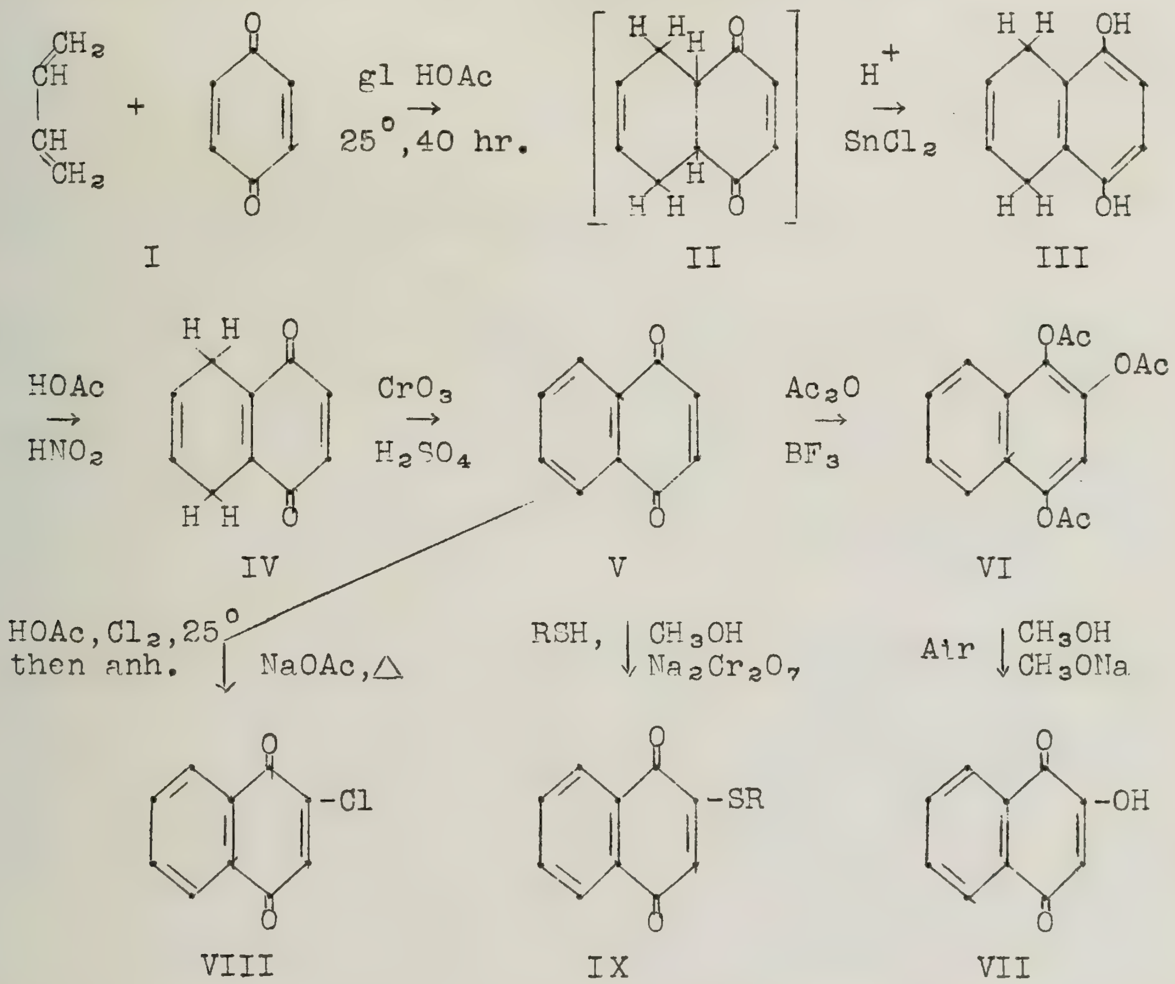
SYNTHESIS OF SOME SUBSTITUTED 1,4-NAPHTHOQUINONES

Reported by Edward A. Sienicki December 9, 1949

Introduction: The investigation of naphthoquinone antimalarials (1) during the past decade has produced a wealth of information concerning the chemistry of 1,4-naphthoquinone and some of its derivatives. This report is confined to a few of the 1,4-naphthoquinone derivatives recently reported.

Series 1(a) Monosubstitution on the Quinoid Ring: The synthesis of 1,4-naphthoquinone (V) (2) and some of its monosubstitution derivatives may be briefly outlined as follows:



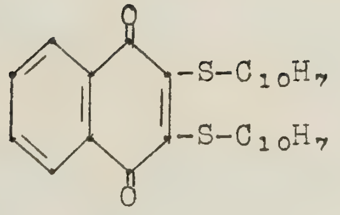
In the preparation of 1,4-naphthoquinone (68-83% yield) according to this procedure, Fieser found the results to be more satisfactory than those which involved the use of α-naphthol (3). Furthermore, whereas previous investigators (4) had employed pressure and higher temperatures for the preparation of 5,8-dihydro-1,4-naphthhydroquinone (III) from 1,4-benzoquinone (I), these conditions were eliminated through the use of glacial acetic acid as a solvent rather than benzene. The two-step oxidation of (III) to (V) was desirable in that it eliminated tar formation which usually

resulted from a one-step oxidation with dichromate. Although earlier synthesis of 2-hydroxy-1,4-naphthoquinone (VII) employed β-naphthol (5) as the starting material, the conversion of (V) to (VII) (76%) through the intermediate 1,2,4-triacetoxynaphthalene (VI) was found to be a much better preparation. The yield of 2-chloro-1,4-naphthoquinone (VIII) from (V) was 75% (6) whereas the yields of the 2-thioalkyl- or 2-thioaryl-derivatives (IX), though they varied with the nature of the mercaptan (7), were higher and more readily obtained than by earlier procedures (8,9). These thio derivatives were also obtainable through a displacement type of reaction (7) with a sodium mercaptide and the 2-chloro-1,4-naphthoquinone. Under anhydrous conditions, a similar reaction may be carried out with sodium methoxide to yield 2-methoxy-1,4-naphthoquinone. It should be pointed out that to obtain 2-alkyl-1,4-naphthoquinones, a convenient procedure is that which employs the corresponding alkylbenzoquinone as the starting material (2).

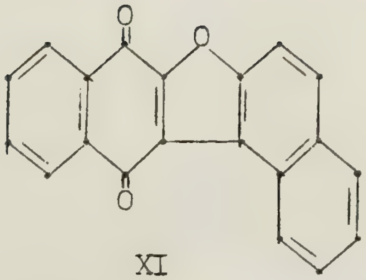
<u>Series 1(b) Disubstitution on the Quinoid Ring</u>: A large variety of disubstituted 1,4-naphthoquinones have been prepared.

The 2-chloro-3-anilino-, 2-chloro-3-hydroxy-, and the 2-chloro-3-thioalkyl-1,4-naphthoquinones may all be prepared from 2-chloro-1,4-naphthoquinone by allowing the latter compound to react with aniline (10), sodium hydroxide (11), and an alkyl mercaptan (7) respectively. The reaction is postulated to be an addition-oxidation process involving the unsubstituted 3-position. In the absence of a specific oxidizing agent, it is probable that the original naphthoquinone acts as the oxidizing agent. This seems to be verified by the low yields often obtained in such instances (7).

The synthesis of 2,3-diphenoxy-1,4-naphthoquinone (12) is accomplished by allowing 2,3-dichloro-1,4-naphthoquinone (6) to react with potassium phenolate in phenol solution. The yield is 96%. A comparable reaction may be satisfactorily carried out using an aryl mercaptan in place of the phenolate (7). Whereas the 2-chloro-3-thioalkyl derivative has been isolated in the reaction between 2,3-dichloro-1,4-naphthoquinone and an alkyl mercaptan, the analogous monoaryl product from an aryl mercaptan (7,13) has never been found even when an excess of the dichloro reactant is present. Conversely, the dithioalkyl derivative has not been obtained from the dichloronaphthoquinone when an alkyl mercaptan is in excess. At this stage of the investigation, β-thionaphthol was allowed to react with 2,3-dichloro-1,4-naphthoquinone with the formation of 2,3-dithio-β-naphthyl-1,4-naphthoquinone (X) (7). Previous work (14) has shown that in a similar reaction between β-naphthol and the dichloro- compound a cyclization takes place with the formation of a furan ring. The Product (XI) is a brazanquinone isomer.



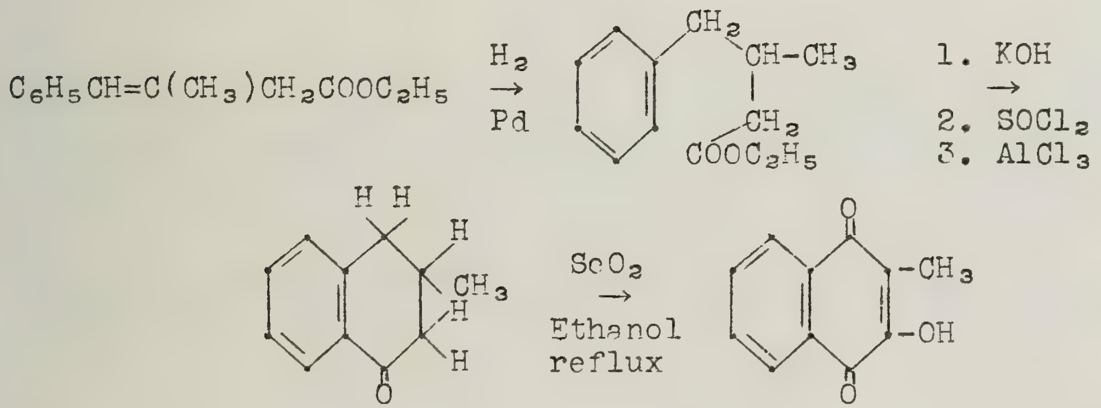
X



XI

Many different 2-hydroxy-3-alkyl-1,4-naphthoquinones have been prepared for testing as antimalarials (15,16). One procedure (2) involves the bromination of the alkylnaphthoquinone in acetic acid medium and then hydrolyzing the 2-bromo-3-alkyl-1,4-naphthoquinone in methyl alcoholic solution to the desired 2-hydroxy-product with an overall yield of 76-84%. In another procedure (17), the 2-hydroxynaphthoquinone is treated with an acyl peroxide in the presence of acetic acid at 90-95°. The yields are not very great but the main by-product, the alkyl acid, may be recovered andrecycled for subsequent runs. A third starts with a benzyl ketone (18) and provides a way to Bz-substituted derivatives. The overall yield is 10%.

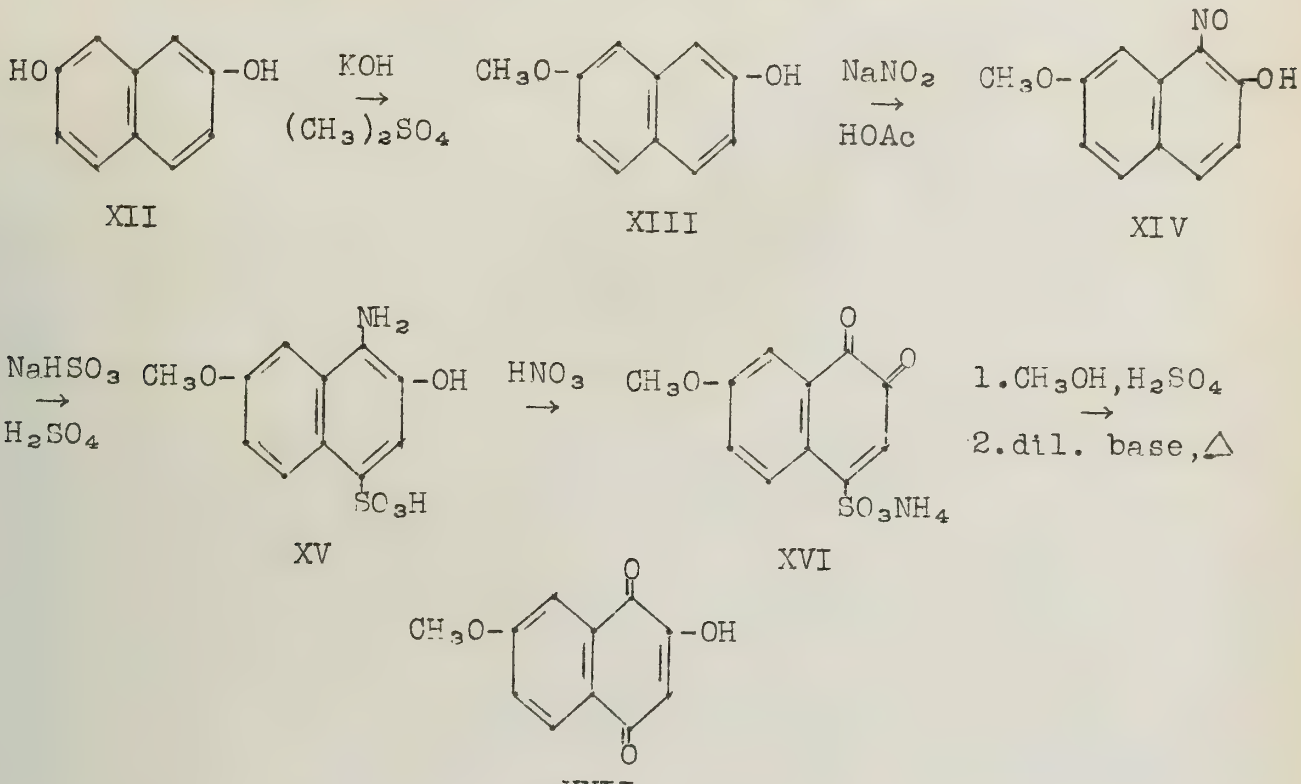
$$C_6H_5CH_2COCH_3 \xrightarrow[BrCH_2COOC_2H_5]{Zn} C_6H_5CH_2COH(CH_3)CH_2COOC_2H_5 \xrightarrow[2.\ \Delta,\ -HCl]{1.\ PCl_5}$$



A fourth synthesis was based on the Mannich reaction (19). In this instance, 2-hydroxynaphthoquinone was allowed to react with formaldehyde in the presence of a primary or secondary amine to yield a 2-hydroxy-3-substituted-aminomethyl-1,4-naphthoquinone.

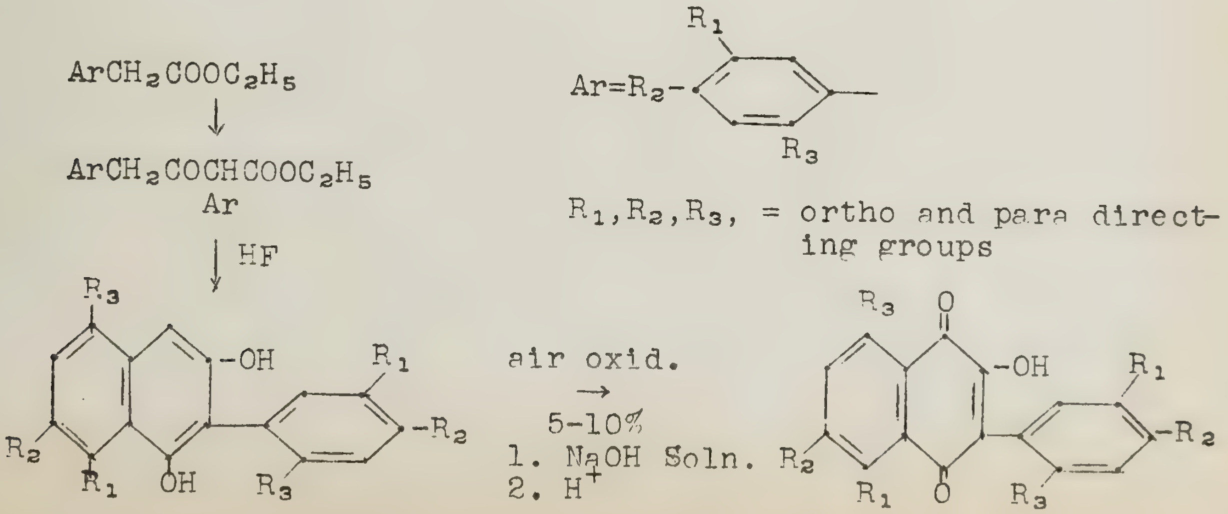
Series 2(a) Mono-Bz-Substituted Derivatives: The synthesis of 7-chloro- and 6-chloro-1,4-naphthoquinone (20,21) was carried out in the following manner: Chloroprene and p-benzoquinone condense to 6-chloro-5,8-dihydro-1,4-naphthoquinone. Subsequent treatment with acetic anhydride and boron trifluoride yielded the 1,2,4-triacetoxynaphthalene. This in turn was hydrolyzed (22) with methyl alcoholic sodium methoxide to the two isomeric chloro-2-hydroxy-1,4-naphthoquinone products. The yields were 30-33%.

A synthesis for 7-methoxy-2-hydroxy-1,4-naphthoquinone (XVII) may be outlined briefly as follows (20,23-26):



The overall yield was 23%. It is of the greatest importance to note that the 3-alkyl derivative of this product can, by means of the Hooker oxidation reaction (27), lead to many different 6- or 7-methoxy-2-hydroxy-1,4-naphthoquinones. Many of these various products are listed in the journals (28).

<u>Series 2(b) Poly-Bz-Substituted Derivatives</u>: Only one example will be given for this series. It is outlined briefly as follows (29,30).



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THE REARRANGEMENT OF NITROPHENYLSUFONYLGUANIDINES

Reported by R. L. Foster December 16, 1949

The reaction of p-nitrobenzenesulfonyl chloride with guanadine in alkaline solution, followed by reduction of the nitro group, can be used in the preparation of sulfaguanidine. It was found that the literature differed as to the product of the condensation. The expected p-nitrophenylsulfonyl guanidine (I) was obtained in one case (1), but only the p-nitrobenzenesulfonate salt of guanidine was obtained in the other (2).

The reactions were repeated and in the first case a disubstituted guanidine (II) was obtained along with the product reported. In the latter case the salt was obtained and also two compounds containing no sulfur. The compounds were found to be p-nitrophenylguanidine (III) and p,p'-dinitrodiphenylamine. These compounds were products of a decomposition of the mono- and disubstituted guanidines respectively. Study of this decomposition led to a method for preparation of nitrophenylguanidines and nitrated diphenylamines.

Another method for obtaining nitrophenylguanidines is the condensation of the appropriate nitroanilin with cyanamide (3). Nitrated diphenylamines can be prepared by heating nitroanilin with nitrobromobenzene in the presence of Cu_2Br_2 and Na_2CO_3 (4). Thus o-nitroanilin and p-nitrobromobenzene give 2,4'-dinitrodiphenylamine.

Nitrobenzenesulfonyl chloride reacts with guanidine to give nitrophenylsulfonylguanidine (I). This structure is chosen rather than the isomeric one because of the compound's insolubility in alkali. The reaction is the same for o-, m- and p-nitrobenzenesulfonyl chlorides.

$$NO_2C_6H_4SO_2N{=}C\genfrac{}{}{0pt}{}{\diagup NH_2}{\diagdown NH_2} \qquad\qquad NO_2C_6H_4SO_2N{=}\overset{NH_2}{\overset{|}{C}}{-}NHSO_2C_6H_4NO_2$$

I II

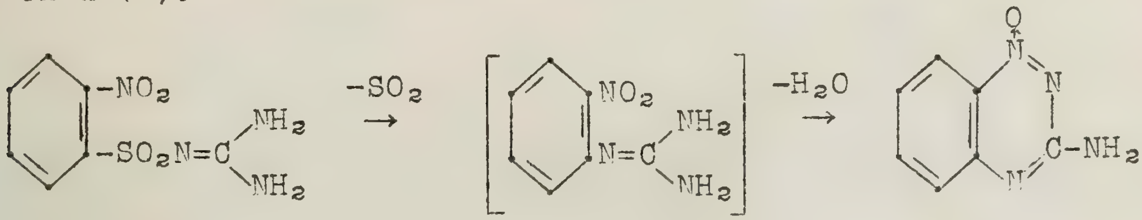
In running the reaction at low temperatures (0-15) a second product, bis-nitrophenylsulfonyl guanidine (II), is also obtained (5). This compound forms a monosodium salt. Mixed disubstituted derivatives (with the two NO_2 groups in different positions) can be prepared by adding another nitrophenylsulfonyl group to the monosubstituted guanidines (6).

p-Nitrophenylsulfonylguanidine undergoes a decomposition in alkaline solution to p-nitrophenylguanidine (III).

$$(p)NO_2C_6H_4SO_2{-}N{=}C\genfrac{}{}{0pt}{}{\diagup NH_2}{\diagdown NH_2} \rightarrow SO_2 + (p)NO_2C_6H_4N{=}C\genfrac{}{}{0pt}{}{\diagup NH_2}{\diagdown NH_2}$$

III

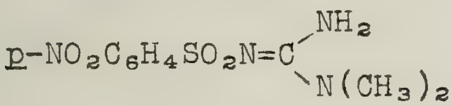
In order to determine the mechanism of this reaction, various guanidine derivatives were studied. o-Nitrophenylsulfonylguanidine (IV) also loses SO_2, but under the conditions of the reaction a cyclic compound, 1-oxy-3-amino-benzo-1,2,4-triazine (V), is obtained (7).



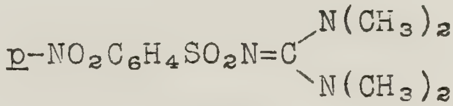
IV V

The meta isomer is stable and does not lose SO_2. Reduction of the nitro group of p-nitrophenylsulfonylguanidine makes the compound stable.

Compound VI, the nitrophenylsulfonyl derivative of asymmetric dimethylguanidine, decomposes although more slowly than unsubstituted guanidines. The tetramethyl derivative (VII) is stable (7).



VI

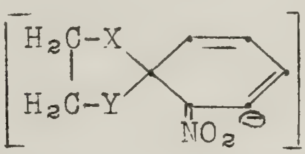


VII

The reaction thus appears not to be a simple elimination of SO_2 but a rearrangement involving the amino group. For the rearrangement to proceed a nitro group in the ortho or para position is necessary to weaken the bond between the sulfur and the aromatic group, and one amino group must be free. The conditions for this rearrangement resemble those of a rearrangement studied by Smiles (8,9).

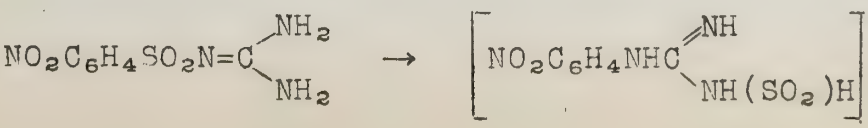
$$\underline{o}\text{-}NO_2C_6H_4XCH_2CH_2YH \rightarrow \underline{o}\text{-}NO_2C_6H_4YCH_2CH_2XH$$

This rearrangement is explained by the formation of the cyclic intermediate shown below. The quinoid structure is consistant with the color observed during the rearrangement.

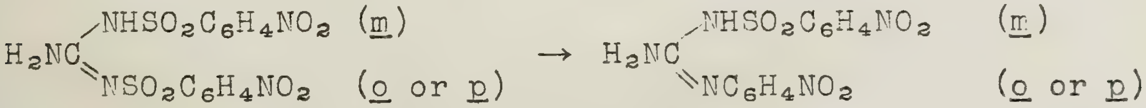


(10)

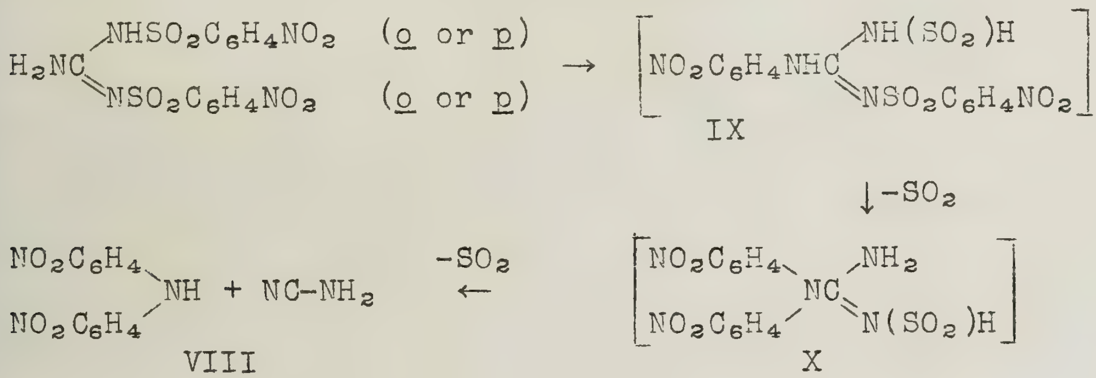
Applying this rearrangement to the guanidine derivatives, an aminosulfinic acid is the intermediate product. The aminosulfinic acid is unstable and loses SO_2.



The rearrangement of bis-nitrophenylsulfonyl guanidines is more complicated. When the nitro group of one of the substituent groups is in the meta position, that group is stable and does not lose SO_2.

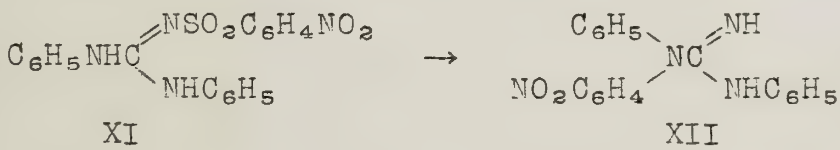


When the nitro groups are ortho or para and both groups migrate, the product is a dinitrodiphenylamine (VIII). The product can be explained by the mechanism postulated.



The aminosulfinic acids are of course unstable but the other intermediates (IX and X after loss of SO_2) have been prepared and are found to decompose in alkaline solution to give dinitrodiphenylamine (VIII).

The rearrangement can occur when there is one substituent on each amino group. The o- and p- nitrophenylsulfonyl derivatives of symmetrical diphenylguanidine (XI) rearrange to give XII.



The yields obtained in this rearrangement are excellent. The liberation of SO_2 is generally quantitative with the isolation of product nearly so. The ortho nitro compounds were generally obtained in lower yields.

This reaction is not limited to guanidine but can be represented more generally (11).

$$ArSO_2{-}N{=}\overset{X}{\overset{|}{C}}{-}NH_2 \rightarrow ArN{=}\overset{X}{\overset{|}{C}}{-}NH_2 \quad (X = OH,\ OR,\ SH,\ SR \text{ or } R)$$

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RECENT REACTIONS OF DIAZOMETHANE AND ITS DERIVATIVES

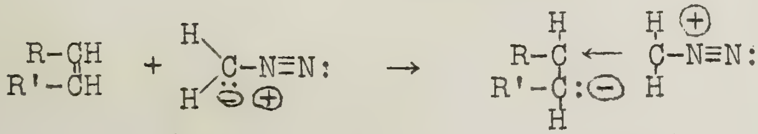
Reported by Richard J. Hellmann   December 16, 1949

The reactions of diazomethane and its derivatives cover a broad field. This field has been reviewed (1,2) recently; therefore, only latest work will be considered in this seminar.

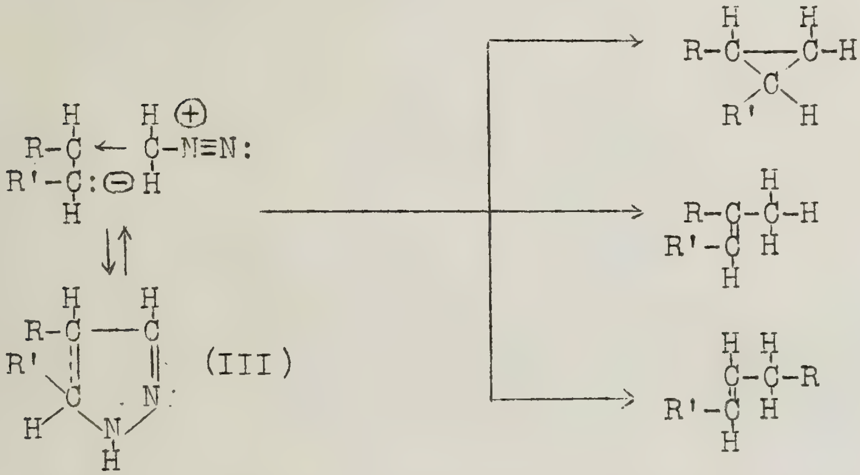
A. The Attack of Diazomethane on Unsaturated Linkages.

The attack of diazomethane and its derivatives on unsaturated carbon-carbon linkages has received attention from many workers.

Eistert (2) gives the following probable mechanism for this attack:



(I) (II)



(III) (IVA) (IVB) (IVC)

The addition probably begins with the entering of the lone electron pair of the extreme resonance form of diazomethane (I) into the double bond, whereby the diazonium betaine (II) is formed. This intermediate product can stabilize itself in the following ways:

1. By the migration of a proton from the methylene group of the diazomethane with the formation of a pyrazoline ring (III).
2. By spliting off nitrogen to form one of three products.
   (a) A three-membered ring (IVA).
   (b) A methyl substituted product by anionic migration of a hydrogen atom (IVB).
   (c) Or the homologous product by anionic migration of the R-group (IVC).

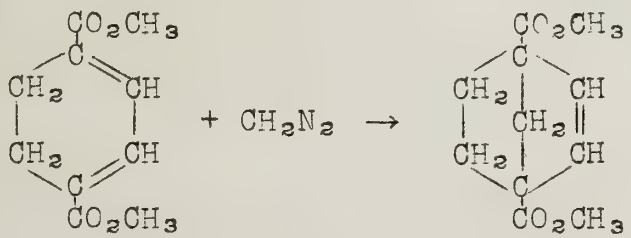
All of these possibilities have been observed experimentally.

Many types of unsaturated compounds such as acetylene, ethylene and substituted ethylenes, α,β-unsaturated esters, acids, aldehydes and ketones, <u>o</u>-quinones, and even some aromatic rings react with diazomethane, usually forming the pyrazole or pyrazoline derivative as the case may be. These reactions have been know for some time (1,2,3).

Of late, the following additions have been made to this knowledge:

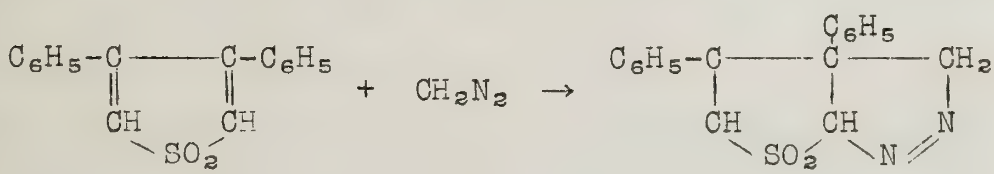
D'yakonov (4) found that while there was no reaction between vinyl butyl ether and diazomethane under ordinary conditions, when the two were heated together in a sealed tube at 90-100° for two days, 4-butoxypyrazoline was formed in 55% yield. This may indicate that perhaps certain other compounds, with which diazomethane seemingly does not react, can react under more drastic conditions.

Conjugated dienes, in general, seem to add diazomethane in the 1,2 manner, giving a pyrazoline (5). However, if the carbon atoms in the 1 and 4 positions are adjacent to negative groups, such as $-COOC_2H_5$ then 1,4 addition is observed (6).



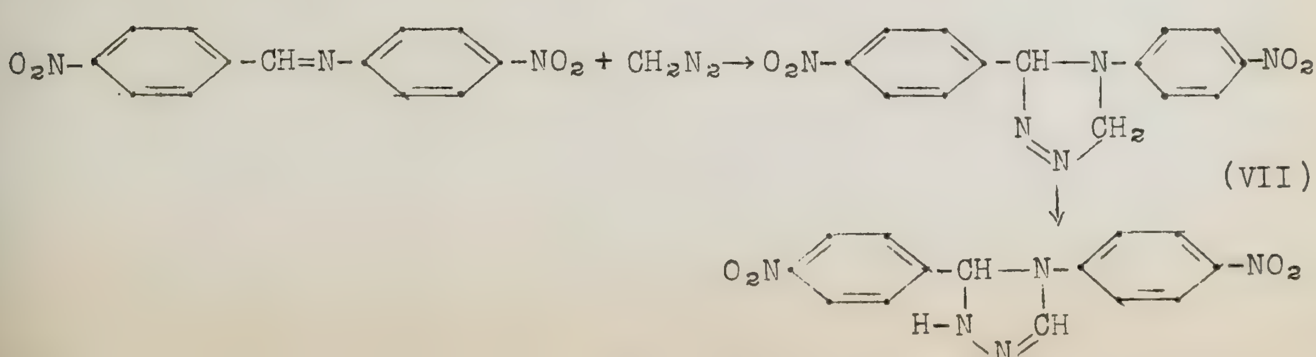
(V)

The addition of diazomethane to unsaturated cyclic sulfones does not take place unless the sulfone is included in a system of two conjugated double bonds. In this case 1,2 addition occurs producing the pyrazoline derivatives in good yields (7). For example:



77% (VI)

Mustafa (8) has observed that when certain nitro-anils are treated with diazomethane or its diphenyl derivative, 1,2,4-triazolines are formed. For example:



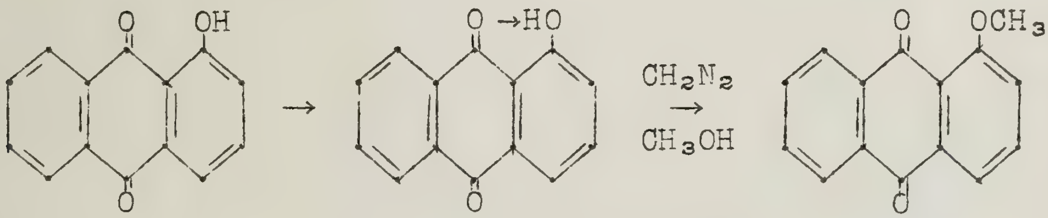
(VII)

B. The Attack of Diazomethane on Phenolic Hydroxyl Groups.

While diazomethane has long been used in the preparation of methyl ethers, there are certain hydroxy compounds which are stable towards ethereal diazomethane. It is now known, however, due to the work of Schoenberg and Mustafa (9,10), that those compounds whose stability is explained by chelation, for instance o-hydroxy ketones and o-hydroxy anils, are readily methylated if methyl alcohol is also present. The effect of methyl alcohol is ascribed to its opening of the chelate ring system, thus rendering the o-hydroxy group free. Furthermore, it is believed that diazomethane reacts with lower alcohols to give the powerful alkylating agent $CH_2=N-NHOR$ or $CH_3-N=NOR$.

$$\begin{aligned} CH_2N_2 + ROH &\rightarrow CH_2=N-NH-OR \text{ or } CH_3-N=N-OR \\ CH_3-N=N-OR + Ar-OH &\rightarrow ArOR + CH_3-N=N-OH \end{aligned} \qquad \text{(VIII)}$$

For example:



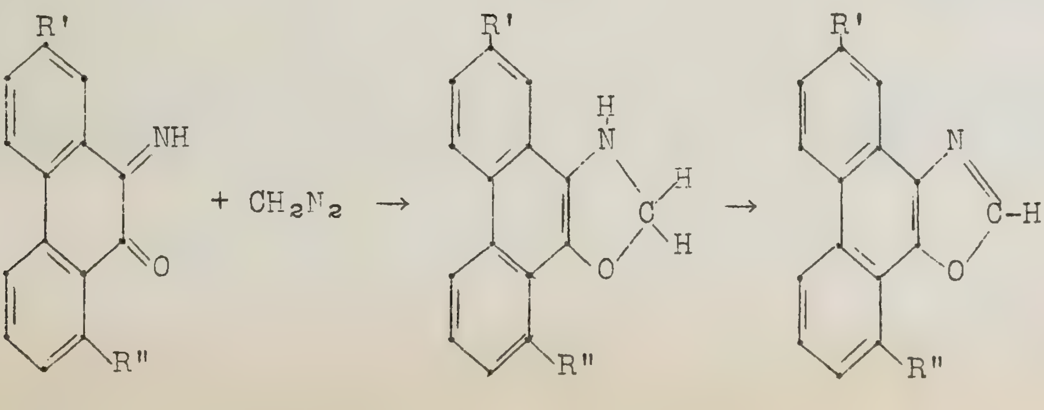
(IX)

This sort of action had been observed earlier by Arndt (11) but no explanation was given.

Schoenberg also reported (9) that when 4,4'-dihydroxy-α,β-dietheyl stilbene was treated with ethereal diazomethane in the presence of n-propyl alcohol, the di-n-propyl ether was obtained. However, Gerber and Curtin duplicated this work and obtained only the mono- and di-methyl ether (12).

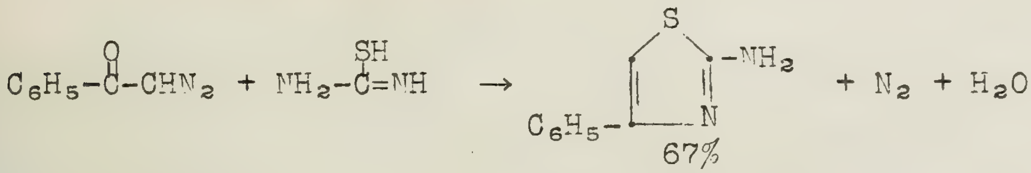
C. Miscellaneous Reactions of Diazomethane.

Some o-quinones react with diazomethane or its derivatives, forming methylene ethers (9,13,14). When this reaction was applied to phenanthraquinoneimine, it was found that phenanthroxazole was formed (15).

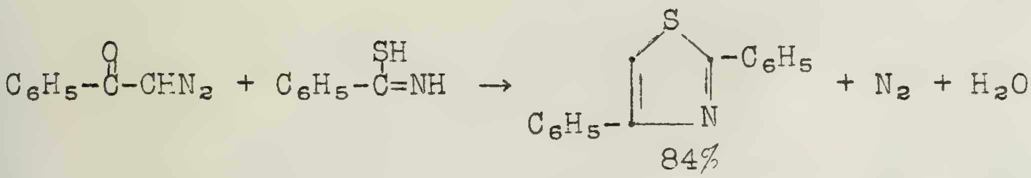


(X)

In another interesting case, diazoketones have been found to react with thioamide derivatives to give substituted thiazoles (16).

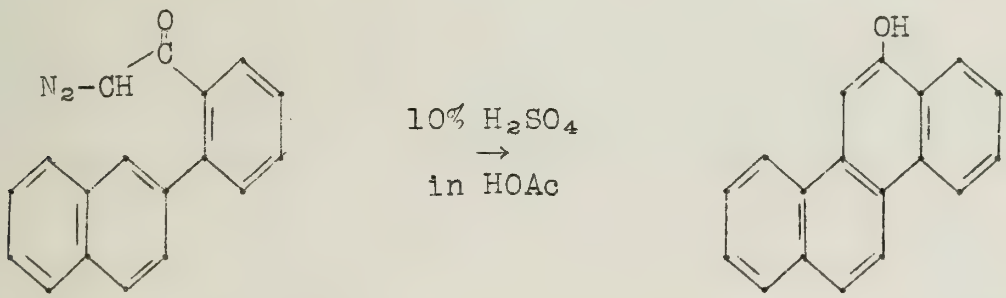


(XI)



(XII)

Cyclization of a diazoketone has also been accomplished (17). However, the only instance of this type of cyclization as yet reported has been the cylization of 2-(o-diazoacetylphenyl)-naphthalene to 2-chrysenol, through the use of 10% sulfuric acid in acetic acid.



(XIII)

Another unusual reaction is that of diazomethane and N-diacyl compounds. Certain of these N-diacyl compounds are stable toward ethereal diazomethane but are converted into the corresponding mono-acyl compounds by an ether-methyl alcohol diazomethane solution (18).

Diazomethane has also been used to prepare bromomethyl ketones from acid bromides (19) and to prepare methyl esters from the ammonium salts of the corresponding acids (20). It has been found recently also that diazoacetophenone reacts with salts of certain heterocyclic amines to produce the corresponding phenacyl quarternary salts (21).

In conclusion mention should be made of the excellent procedures developed by Wilds and Meader (22) which make it possible to use the Arndt-Eistert reaction with higher diazohydrocarbons.

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RECENT ADVANCES IN AMINO ACID SYNTHESES

Reported by Cal Y. Meyers December 16, 1949

In the past two years there has been a remarkable number of improvements in the preparation and isolation of racemic and optically active amino acids. This seminar is an attempt to review briefly the more important developments.

Part I. Preparation of Racemic Amino Acids.

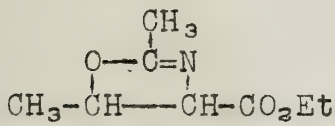
Threonine (β-hydroxy-α-amino-n-butyric acid)

Until recently the best threonine synthesis (1) gave only a 20% overall yield. The low yield was due, in general, to the failure to convert the attainable allothreonine to its diastereoisomer, threonine, which is the biologically active form. The workers at Merck (2, 3) have succeeded in overcoming this barrier.

1) $CH_3COCH_2CO_2Et \xrightarrow{C_6H_5N_2Cl} CH_3COCH(N_2C_6H_5)CO_2Et$

$\xrightarrow[\text{acylation}]{\text{reductive}} CH_3COCH(NHCOCH_3)CO_2Et \xrightarrow[PTO_2]{H_2} CH_3CHOHCH(NHCOCH_3)CO_2Et$

80-85% allo-type

$\xrightarrow{SOCl_2}$  $\xrightarrow[C_6H_5NH_2]{HCl} CH_3CHOHCHNH_2CO_2H$

83% dl-Threonine

Upon purification the overall yield was 57% and microbiol. assay showed 100% purity. Starting with N-benzoylallothreonine a 70% overall yield of threonine was obtained by this sequence. The important point is the single inversion involved.

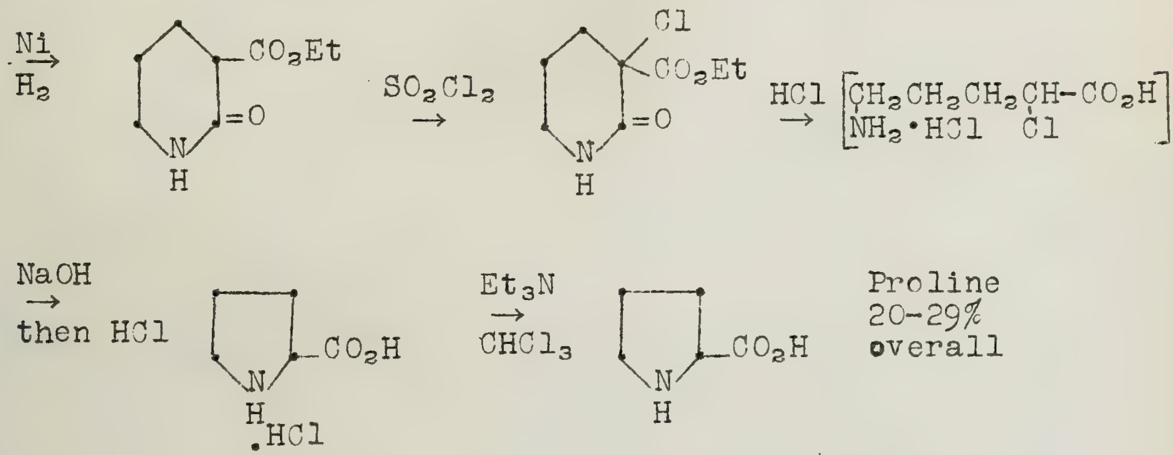
2) In 1938 it was noted (4) that methyl hypobromite and crotonic acid, after a series of steps, yielded allothreonine and 6-8% threonine. Since methyl hypobromite adds unidirectionally, Carter, in 1936, suggested using isocrotonic acid (geom. isomer of crotonic acid) to obtain mainly threonine.

This scheme was recently carried through at Merck (3) and a 36% yield of threonine was obtained. The acid piperidide was studied most thoroughly since it is easily prepared and purified. By this means a 58.2% yield of threonine was realized, making this method of practical importance.

Proline (pyrrolidine-2-carboxylic acid)

Proline is alcohol soluble; all of the heretofore recorded syntheses use silver salts to remove the halides and the copper salt of proline for purification. So the usual preparation is tedious and costly. The method described here (5) is simple and practical:

$$CH_2{=}CHCN + CH_2(CO_2Et)_2 \xrightarrow{NaOEt} NCCH_2CH_2CH(CO_2Et)_2$$



It is interesting to note the similarity between these reactions and those presented by Moe and Warner (11) and Albertson and Archer (18) for ornithine.

Lysine (α,ϵ-diaminocaproic acid)

The series of lysine preparations through 1948 have been well summarized in a previous seminar (6). But in the past few months practical and interesting methods have been presented (7, 8, 9).

Rogers, Emmick, et. al. (7) utilize dihydropyran in a 40% overall lysine synthesis, very similar to that discovered by Gaudry, et. al. (10).

Sayles and Degering (8) have prepared lysine from butylene chloride, *n*-butyl bromide, and *n*-nitrobutane, but the yields are very low.

Moe and Warner (9, 11) have synthesized tryptophan (11), ornithine (11), and lysine (9), using acrolein and acetamidomalonic ester (12). Glutamic acid (11) is made from acrolein and cyanoacetic ester.

1) Tryptophan (β-3-indole-α-aminopropionic acid)

Most of the newer methods (13-16) employ gramine as starting material, but a good method by Hegedus (17) utilizes acetoacetic

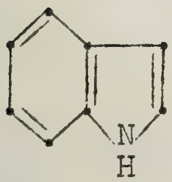
ester. Moe and Warner claim a 43% yield of tryptophan:

$$CH_2{=}CHCHO + CH_3CONHCH(CO_2Et)_2 \xrightarrow{NaOEt} \underset{\text{I}}{CH_3CONHC(CO_2Et)_2CH_2CH_2CHO}$$

$$\xrightarrow{PhNHNH_2} \underset{\text{II}}{CH_3CONHC(CO_2Et)_2CH_2CH_2CH{=}NNHPh}$$

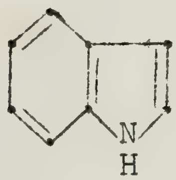
25% yield with $\xrightarrow{}$ (BF$_3$ (gl HOAc

73% yield with H_2SO_4



$CH_2C(NHCOCH_3)(CO_2Et)_2$ 1) acidification 2) decarboxylation $\longrightarrow$ 3) hydrolysis

[same intermediate as Snyder and Smith (13)]



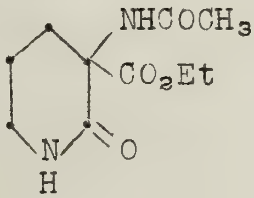
$CH_2CHNH_2CO_2H$

Tryptophan 43%

2) Ornithine (α,δ-diaminovaleric acid)

Albertson and Archer (18) published an excellent synthesis of ornithine using the cyanoethylation product of acetamidomalonic ester. Moe and Warner (11) using II followed the same route:

II $\xrightarrow[H_2]{Ni}$



$\xrightarrow[-CO_2]{H_3O^{\oplus}}$ $NH_2(CH_2)_3CHNH_2CO_2H$

quantitative 61% overall

3) Lysine

Moe and Warner take advantage of I to prepare lysine:

$$\text{I} \quad -CH_2CHO \xrightarrow{HCN} -CH_2CHOHCN \xrightarrow{Ac_2O} [-CH_2CHOAcCN] \rightarrow$$

$$[-CH{=}CHCN] \xrightarrow[Ac_2O]{H_2,\ PtO_2} -(CH_2)_3NHCOCH_3 \xrightarrow{H_3O^{\oplus}} NH_2(CH_2)_4CHNH_2CO_2H$$

40% overall

4) Glutamic Acid (α-aminoglutaric acid)

This has been synthesized by 1,4-addition of phthalimidomalonic- and acetamidomalonic esters with methylacrylate (19, 20) and acrylonitrile (18). The present synthesis by Moe and Warner utilizes the acrolein-acetamidocyanoacetic ester 1,4-addition product III:

$$\underset{\text{III}}{CH_3CONHCCNCO_2EtCH_2CH_2CHO} \underset{KMnO_4}{\overset{[O]}{\rightarrow}} -CH_2CO_2H \underset{-CO_2}{\overset{H_3O^{\oplus}}{\rightarrow}} HO_2C(CH_2)_2CHNH_2CO_2H$$

<u>Part II. Resolution of Racemic Amino Acids</u>: The foregoing syntheses involve the production of racemic amino acids; biologically the L-form is required for metabolism and its isolation is valuable.

<u>Threonine</u>. The best method appears to be through the N-p-nitrobenzoyl derivative in a metharolic solution of active brucine (21, 22). The L-threonine salt is less soluble.

<u>Tryptophan</u>. The brucine salt of N-acetyl-D-tryptophan in alcoholic solution separates first (23, 24).

<u>Enzymatic Methods</u>. (25-32) Very recently an enzymatic resolution scheme has been presented (25) which should have wide commercial application, as well as academic. Preparations of hog kidneys or beef pancreas enzymatically act on N-acylated DL-amino acids, hydrolyzing only the L-form. The pH is adjusted and in alcoholic solution, the L-amino acid is precipitated, leaving the N-acylated D-form in solution. The D-amino acid is isolated by extraction and hydrolysis. This method gives good yields, is rapid, and produces acids of high optical purity. It has been applied successfully (25) to 13 natural amino acids.

Enzymatic hydrolysis of amino acid esters, producing the active forms has also been announced recently (31, 32).

The use of papain (from the papaw plant) has been used to form the anilide or phenylhydrazide of N-acylated amino acids. The enzyme causes the formation of one of the active forms (26-30).

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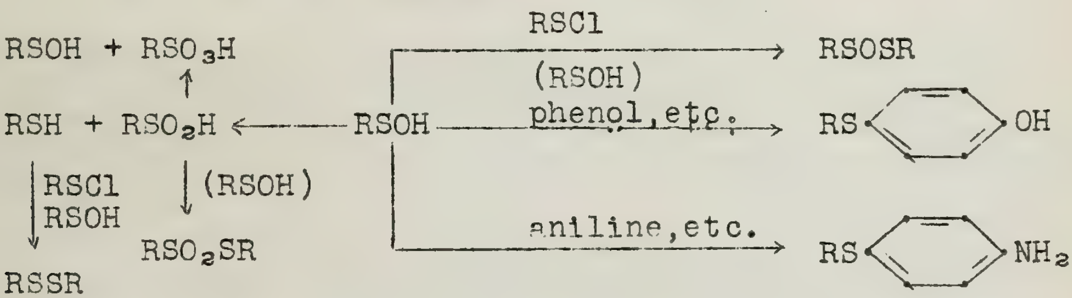
DERIVATIVES OF SULFENIC ACIDS

Reported by Franklin E. Mumford December 16, 1949

I. Sulfenic Acids: Organic compounds of bivalent sulfur which correspond to the formula RSOH are generally called sulfenic acids. Although sulfenic acids have been postulated as intermediates in many reactions (1), only one such acid has been isolated in the free state; namely, 1-anthraquinonesulfenic acid (2). Hydrogen bonding with the keto group in 1-anthraquinonesulfenic acid may explain the stability of this acid. A study is being carried out at the present time with 1-fluorenone sulfur compounds to determine whether this is the case (3). In comparison with the inorganic oxygen acids of sulfur, which are stable only when the sulfur atom displays a maximum valence of six, the sulfenic acids would be expected to be unstable and undergo the following reactions (1).



II. Derivatives of Sulfenic Acids: Many derivatives of sulfenic acids are known. The sulfenyl halides, generally precursors of the other derivatives of sulfenic acids, bear special attention. Aromatic sulfenyl chlorides and bromides may be synthesized by three essentially similar methods involving the action of chlorine or bromine on aryl disulfides (A), thiophenols (B), or aryl benzyl sulfides (C) (4).

A) $ArSSAr + X_2 \rightarrow 2\ ArSX$
B) $ArSH + X_2 \rightarrow ArSX + HX$
C) $ArSCH_2C_6H_5 + 2X_2 \rightarrow ArSX + C_6H_5CHX_2 + HX$

Some restrictions to these methods of synthesis should be noted. Firstly the ease of formation of the sulfenyl halide by the reaction of the disulfide or thiophenol with one molar proportions of halogen seems to decrease in passing from chlorine to iodine. Excess halogen cannot ordinarily be used, of course, since tetra halogen derivatives will form which on hydrolysis yield thiosulfonic acids. Secondly halogenation in the aromatic nucleus might proceed in preference to cleavage of the disulfide linkage. Negative groups in the aromatic nucleus, e.g., nitro, greatly decrease substitution in the nucleus. The use of low temperatures, dilution reagents, and exclusion of light and moisture have also been effective where this problem was encountered (5). 2-Benzothiazolesulfenyl iodide has been synthesized according to method A, but this is the only record of synthesis of a sulfenyl iodide by this means (6).

Kharasch (7) has found that 2,4-dinitrobenzenesulfenyl chloride dissolved in conc. sulfuric acid to give a blood red solution. He attributes the red color to $ArS^{\oplus}$ formed by the following ionization.

$$\text{D) } ArSCl + H_2SO_4 \rightarrow ArS^{\oplus} + HCl + HSO_4^{\ominus}$$

Sulfenyl thiocyanates (RSSCN) (5) may be prepared either by the reaction of a sulfenyl halide with a metal thiocyanate (E), or by reaction of a thiophenol or mercaptan with thiocyanogen (F).

$$\text{E) } RSCl + KSCN \rightarrow RSSCN + KCl$$
$$\text{F) } RSH + (SCN)_2 \rightarrow RSSCN + HSCN$$

Method E is obviously limited by the availability of the sulfenyl halides. Reaction F is widely applicable, and the difficulties associated with the synthesis of sulfenyl halides from mercaptans are not very troublesome in this case.

Sulfenamides have been of interest for some time because of their utility as accelerators in the vulcanization of rubber. Zincke (8,9) recorded the earliest preparation of sulfenamides by the reaction of aromatic sulfenyl halides with ammonia and primary or secondary amines.

$$\text{G) } RSX + 2HNR_2 \rightarrow RSNR_2 + R_2NH_2X$$

Weakly basic amines do not undergo this reaction with ease, if at all. Sulfenyl thiocyanates and sulfenic acid esters may be used in place of the sulfenyl chlorides. Sulfenamides have also been prepared by the reaction of aromatic mercaptans and amines in the presence of oxidizing agents such as hypochlorites, hydrogen peroxide, and potassium ferricyanide (1).

$$\text{H) } ArSH + HNR_2 \xrightarrow{(O)} ArSNR_2 + H_2O$$

It must be mentioned, though, that thiophenols or mercaptans have a strong tendency to form disulfides in the presence of the oxidizing agent, and thus the number of examples of this reaction are not sufficient to evaluate its use in synthesis.

Alkyl and aryl sulfenates (RSOR' where R' may be alkyl or aryl) are isomeric with the sulfoxides, but it has been clearly established that the two classes of substances are different. The sulfenates are generally prepared by the reaction of sodium alkoxides or phenoxides with the sulfenyl halides or sulfenyl thiocyanates (1).

$$\text{I) } RSCl + NaOR' \rightarrow RSOR' + NaCl$$

The reaction of alkyl hypochlorites with mercaptides does not give sulfenic esters, as might be expected, but the disulfides (10).

$$\text{J) } 2RSNa + R'OCl \rightarrow RSSR + R'ONa + NaCl$$

The only known sulfenic acid, 1-anthraquinonesulfenic acid, may be esterified directly.

The main products of the hydrolysis of sulfenyl chlorides are the sulfenic anhydrides (RSOSR).

$$\text{K)}\quad ArSCl \xrightarrow{HOH} ArSOH \xrightarrow{ArSCl} ArSOSAr$$

Conc. hydrochloric acid converts the anhydrides to chlorides, while a freshly prepared ammoniacal solution of the anhydrides treated with lead acetate precipitates a blue substance, presumably the lead salt, which rapidly becomes colorless. Zincke suggested that such reactions implied an amphoteric character for sulfenic acids.

$$\text{L)}\quad RSOSR \xrightarrow{HOH} RSOH \begin{cases} \xrightarrow{HCl} RSCl \\ \xrightarrow{Pb^{++}} (RSO)_2Pb \end{cases}$$

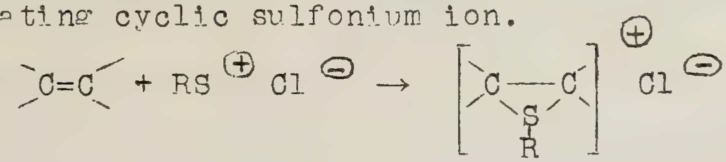
The sulfenyl chlorides, thiocyanates, amides, esters and anhydrides are colorless to yellow or red compounds and distillable <u>in vacuo</u>. Reactions of the derivatives of sulfenic acids may be found in reference <u>1</u>.

Recently Foss (11) has suggested that a bivalent organic sulfur compound may be classified as a sulfenic acid derivative by virtue of its ability to take part in nucleophilic displacement reactions which involve cleavage into $RS^{\oplus}$ and $X^{\ominus}$. As this is by far the most common type of dissociation which sulfenic acids display, this criterion is suitable for purposes of classification. Such a classification greatly extends the field of sulfenic acid derivatives. Thus thiolsulfonate esters ($ArS^{\oplus}SO_2Ar^{\ominus}$), sulfenyl arylthiosulfonates ($ArSS_2O_2Ar$), sulfenyl thiosulfates ($ArS^{\oplus}S_2O_3^{\ominus}$), sulfenyl di-O-alkylmonothiophosphates ($ArSSPO(OR)_2$), sulfenyl alkanethiolsulfonates ($ArSS_2O_2R$), and esters of thiosulfuric acid, which react as sulfenyl sulfites ($ArS^{\oplus}SO_3^{\ominus}$) may be included as derivatives of sulfenic acids. Many new derivatives may be expected, such as the sulfenyl selenocyanates just reported by Rheinboldt and Giesbrecht (12).

III. <u>Use of 2,4-Dinitrobenzenesulfenyl Chloride (S.C. Reagent) as an Analytical Reagent</u>: Billman (13,14) reported the use of 2-nitro- and 2,4-dinitrobenzenesulfenyl chloride for the identification of amines several years ago. However, 2,4-dinitrobenzenesulfenyl chloride will react with practically all electron-rich substances -- olefins, alcohols, mercaptans, amines, anions -- to give products that are useful for identification, and thus this reagent has great possibilities for analytical and synthetic work. Kharasch has recently reported the use of S.C. Reagent in characterizing cyclic olefins (15), olefins (16), and aromatic compounds (17,18).

Formerly S.C. Reagent was best prepared by the hazardous, high temperature chlorinolysis of 2,4-dinitrophenyl disulfide. However, its synthesis is now easily achieved by cleavage of the disulfide with chlorine in the presence of a Friedel-Crafts type catalyst, particularly sulfuric acid, at 20-30° (17,18).

The addition of sulfenyl chlorides is believe to proceed through a resonating cyclic sulfonium ion.

M) 

The sulfonium ion may (a) add the chloride ion to yield the β-chloro sulfide, (b) eliminate a proton to form the vinyl sulfide, or (c) react with a solvent, such as acetic acid, to form the β-acetoxy sulfide. The products which result may thus be predicted by Markownikoff's rule. However exceptions are found in the cases of propylene and 2-pentene in which only sixty-five percent of the product obtained is the Markownikoff adduct, the rest of the product being the non-Markownikoff adduct.

With the S.C. Reagent aromatic compounds yield the aryl 2,4-dinitro sulfides. Reaction with active aromatic nuclei, such as resorcinol and dimethylaniline, proceeds without a catalyst. With less active aromatic nuclei the reaction proceeds in good yield only in the presence of aluminum chloride, while reaction with thiophene may be accomplished using stannic chloride. A critical amount of catalyst is required (19). The mechanism is not definitely established for the attack of the S.C. Reagent on aromatic systems, but it may be via the sulfenium ion. Kinetic studies related to these reactions are under way at the present time (20).

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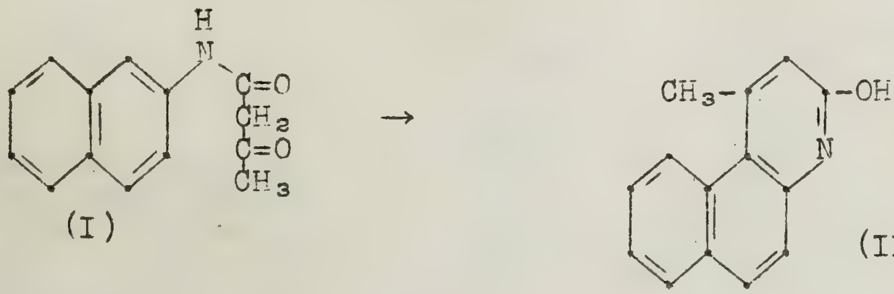
THE COMBES CYCLIZATION METHOD
ANOMALOUS ORIENTATION OF β-NAPHTHYLAMINE DERIVATIVES

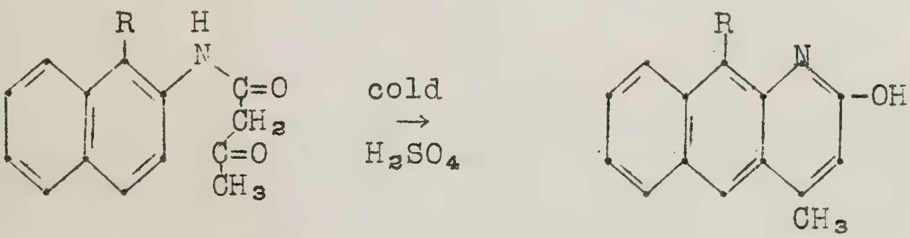
Reported by Rudolph F. Fischer | January 6, 1950

Ring closure on an aromatic nucleus may be considered to occur by an intramolecular electrophilic attack, directed primarily to the ortho position for steric reasons. In the β-naphthylamine series, two ortho positions are available, and whether cyclization is angular or linear is determined by the relative ease of formation of the corresponding intermediates (1). Thus acetoacet-β-naphthalide (I) forms only the angular 4-methyl-5,6-benzocarbostyril (II).



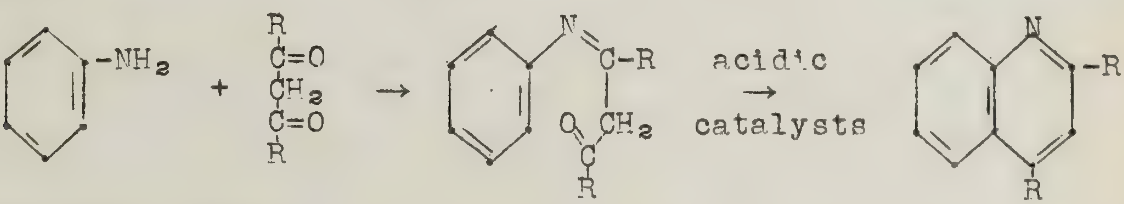
(I) (II)

If a group is present in the 1-position, some cases of linear closure are known (2). For example, the reaction



proceeds in good yield if R is CH_3 or Br. In general, however, the conventional cyclizations will occur at position-1 if it is not blocked.

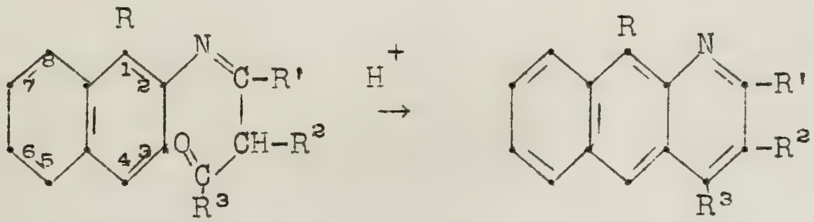
Within the past few years, several investigators have had occasion to use the Combes method (3) on β-naphthylamine derivatives. This method involves the cyclization, employing acidic catalysts, of the anils formed from aromatic amines and 1,3-dicarbonyl compounds.



R = H, CH_3, C_6H_5

The following facts have been determined:

1. If protonic catalysts are used on β-naphthylamine derivatives, the orientation is almost entirely linear, even if no substituent is present in the 1-position.



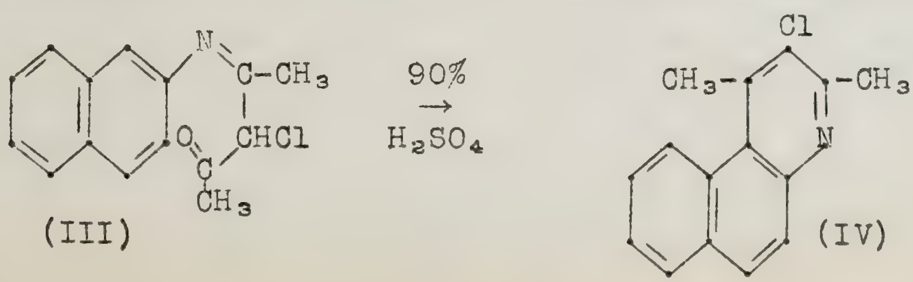
Substituents	Catalyst	Yield	Reference
a. $R=R^2=H$; $R'=R^3=CH_3$	HF	96%	4
	H_2SO_4	83%	4
b. $R=R'=H$; $R^2=R^3=CH_3$	HF	80%	5
c. $R=R'=R^2=H$; $R^3=CH_3$	HF	43%	5
d. $R=R^2=H$; $R'=R^3=C_6H_5$	H_2SO_4	82% (8% angular)	8
e. $R=R'=R^3=CH_3$; $R^2=H$	HF	96%	4
f. $R=Br$; $R'=R^3=CH_3$; $R^2=H$	H_2SO_4	72%	8
g. $R=R^2=Cl$; $R'=R^3=CH_3$	H_2SO_4	not given	6
h. $R=Cl$; $R^2=H$; $R'=R^3=CH_3$	H_2SO_4	(ca.) 50%	6
i. (same as (a) but with Br in 3-position)	H_2SO_4	none	8

Examples (a.) through (d.) are theoretically important, since they offer opportunity for angular cyclization. The 5- and 6- chloro and 6- bromo compounds in which R and R^2 are H; R' and R^3 are CH_3 are also found to cyclize in the linear manner (6), as are the two phenanthrene derivatives which have been investigated (5).

2. The corresponding anil of α-naphthylamine does not cyclize under conditions which readily cyclize the β-derivative (5).

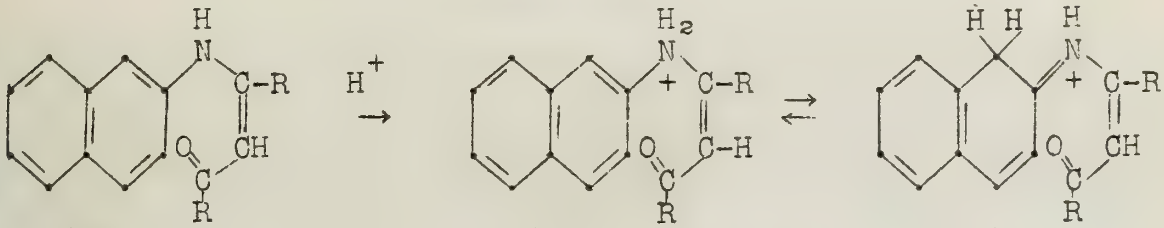
3. If acidic, non-protonic catalysts (e.g. $ZnCl_2$) are employed, the closure is exclusively angular (7,5).

4. An exception to rule 1 has been found (5) in the following compound, (III), which yields only the angular compound (IV).



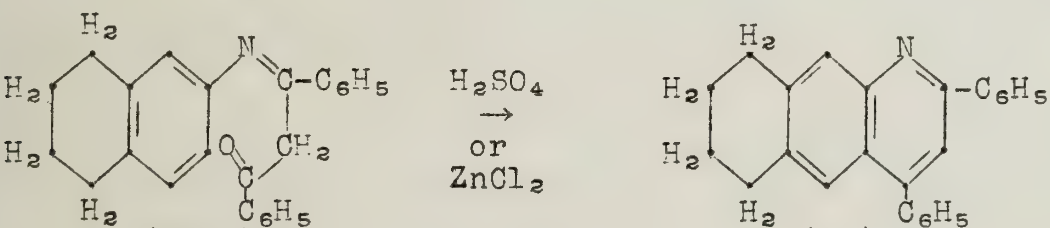
(III) (IV)

Huisgen (8) has proposed a theory which seems to account for these facts. He points out that it is the proton-catalyzed reaction which is anomalous and suggests that coordination of the proton by the nitrogen atom is the cause of the unreactivity at the 1-position.



(V) (VI) (VII)

He is also careful to indicate that a tautomerism such as that represented in (VI) and (VII) probably cannot exist in the benzene series, since the aromatic bonds are not "fixed". This would tend to indicate that the distinction between the two types of acidic catalysts should disappear in the benzene series. He finds support for this in the fact that the anil (VIII) formed from β-amino tetralin and dibenzoylmethane gives the same tetramethylene-diphenyl quinoline (IX) with both types of catalyst.



(VIII) (IX)

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RECENT DEVELOPMENTS IN THE CHEMISTRY OF THE FLUOROACETYLACETONES

Reported by Montfort A. Johnsen   January 6, 1950

A. Introduction

The ability of acetylacetone to enolize and produce chelate salts of surprising stability is of interest. However, the boiling points of most of these substances are so high that distillation cannot be used for their separation or purification. Since replacement of two or more hydrogens on a given carbon atom by fluorine enhances both the thermal stability and volatility of organic molecules, the formation of fluoroacetylacetone chelates seemed a logical method for overcoming this limitation.

B. Fluoroacetylacetones

I. 1,1,1-Trifluoroacetylacetone.--Until recently, the best method for the preparation of this compound involved about ten steps (1,2,3), starting with 1,1,1-trichloropropene and ending with the Claisen Condensation of trifluoroacetic ester and acetone over sodium ethoxide. Overall yields were, of course, very low. In 1949, Johnsen (4), using two procedures of four steps each, was able to obtain the diketone in overall yields of about 70%. These methods will now be outlined:

Synthesis A.

$$CCl_2{:}CCl\cdot CCl{:}CCl_2 + SbF_3 + SbF_3Cl_2 \xrightarrow[135^\circ]{90.psi.g.} 2SbCl_3 +$$

$$CF_3\cdot CCl{:}CCl\cdot CF_3 \quad (82\%\ \text{Yield}) \quad (5).$$

$$3CF_3\cdot CCl{:}CCl\cdot CF_3 + 4KMnO_4 + 8KOH \xrightarrow[70^\circ]{60\ \text{hours}} 6CF_3\cdot CO_2K +$$

$$6KCl + 4MnO_4 + 4H_2O \quad (94\%\ \text{Yield}) \ (5).$$

$$2CF_3\cdot CO_2K + H_2SO_4 + 2C_2H_5OH \xrightarrow[45^\circ]{15\ \text{min.}} CF_3\cdot CO_2C_2H_5 +$$

$$K_2SO_4 + 2H_2O \quad (98\%\ \text{Yield})$$

$$CF_3\cdot CO_2C_2H_5 + (CH_3)_2CO \xrightarrow[\text{reflux over NaOEt}]{50\ \text{hours at}} CF_3\cdot CO\cdot CH_2\cdot CO\cdot CH_3 +$$

$$C_2H_5OH \quad (91.3\%\ \text{Yield}).$$

In contrast to the 91.3% yield of this last reaction it is interesting to note that optimum yields for the condensation of ethyl acetate and acetone over sodium ethoxide are between 30 and 35% (10).

Synthesis B.

Potassium trifluoroacetate was acidified, the acid removed as the 80.5% acid in water azeotrope, and made anhydrous by treatment with 100% sulfuric acid. The anhydride is not easily formed when the usual dehydrating agents are used, but magnesium perchlorate is a satisfactory reagent.

$$2CF_3\cdot CO_2H + (Mg(ClO_4)_2) \xrightarrow[\text{50 hours at reflux.}]{35^\circ} (CF_3\cdot CO)_2O \quad \text{(89\% Yield)}$$

The anhydride can then be condensed with acetone, using boron trifluoride:

$$(CF_3CO)_2O + (CH_3)_2CO \xrightarrow[\text{Add } BF_3 \text{ for four hours.}]{-20^\circ} CF_3\cdot CO\cdot CH_2\cdot CO\cdot CH_3 + CF_3\cdot CO_2H \quad \text{(73\% Yield)}$$

The diketone boils lower than acetylacetone and has a similar odor. A large number of chelate compounds, such as copper (II) 1,1,1-trifluoroacetylacetonate, have been prepared. It was found (4) that ammonium 1,1,1-trifluoroacetylacetonate sublimes as low as 55° at 630. mm., and rapidly at room temperature under vacuum. This, then, offers a simple method for the preparation of extremely pure samples of both the diketone and its chelates. Ammonium acetylacetonate, on the other hand, chars upon heating, indicating a greater tendency for the formation of chelate complexes with the fluorinated diketone.

II. 1,1,1,5,5,5-Hexafluoroacetylacetone.--Trifluoroacetic ester was used to prepare 1,1,1-trifluoroacetone, as follows:

$$CF_3\cdot CO_2C_2H_5 + CH_3\cdot CO_2C_2H_5 \xrightarrow[\text{ether}]{NaOEt} CF_3\cdot CO\cdot CH_2\cdot CO_2C_2H_5 + C_2H_5OH \quad \text{(80\% Yield)}$$

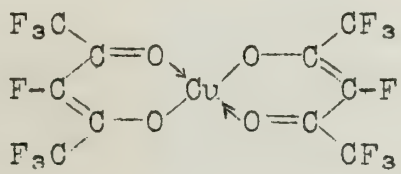
$$CF_3\cdot CO\cdot CH_2\cdot CO_2C_2H_5 + H_2O \xrightarrow[H_2SO_4]{10\%} CF_3\cdot CO\cdot CH_3 + CO_2 + C_2H_5OH \quad \text{(98\% Yield)}$$

The ketone is then condensed with trifluoroacetic ester over sodium ethoxide as follows:

$$CF_3\cdot CO\cdot CH_3 + CF_3\cdot CO_2C_2H_5 \xrightarrow[\text{reflux over NaOEt}]{\text{35 hours at}} CF_3\cdot CO\cdot CH_2\cdot CO\cdot CF_3 + C_2H_5OH \quad \text{(72\% Yield)}$$

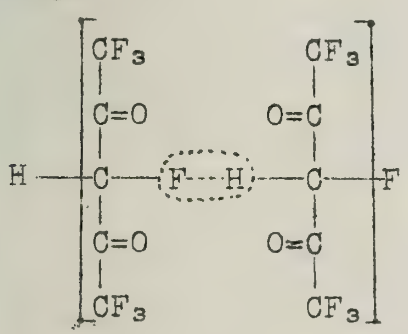
Other modifications of this synthesis have been used (7), such as the use of sodium triphenylmethoxide as a catalyst (6). A few chelate compounds of the diketone, such as copper (II) 1,1,1,5,5,5-hexafluoroacetylacetonate, have been prepared. The ammonium compound has not been made, although it has been suggested that this chelate should sublime very rapidly in air at room temperature (4). Inner complexes formed from this diketone possess the unique property of forming liquid hydrates with water (2).

III. 1,1,1,3,5,5,5-Heptafluoroacetylacetone.--The structure of copper (II) 1,1,1,3,5,5,5-hexafluoroacetylacetonate may be pictured as follows:



If any hydrogen atoms were present in such a molecule, intramolecular H-F bonding could occur. The perfluorinated structure, however, cannot have such association, hence a lowered boiling point would be expected.

Although the synthesis of this compound has been attempted (8), using, presumably, trifluoroacetic ester and 1,1,1,3-tetrafluoroacetone, only high molecular weight tarry products were finally obtained. The probable course of this reaction involves polymerization as the last step, and the following mechanism is proposed:



The bond between fluorine and a monofluorinated carbon has been shown to be a weak one. The presence of two adjacent carbonyl groups further increases the mobility of the fluorine atom. For this reason hydrogen fluoride is probably split out to form a condensation polymer. The tendency to liberate hydrogen fluoride is also enhanced by the extremely basic reaction medium.

C. Uses of Fluoroacetylacetones

The successive replacement of methyl groups in acetylacetone with trifluoromethyl groups has been observed to cause a profound decrease in boiling point, coupled with enhanced thermal and chemical stability. A similar trend has been found with the chelate salts of these diketones. The following table gives some physical constants for the diketones and corresponding copper chelates:

	Diketone	Copper (II) Chelate Compound	
	B.P.	M.P.	Sublimation Point
"Normal"	139.6°C.	233°(d).	d.
1,1,1-Trifluoro-	107.	190.4	128°
Hexafluoro-	64.	112.	75°

Processes involving fractional distillation, fractional sublimation, or fractional decomposition of fluoroacetylacetonates offer considerable promise as separation procedures for difficultly separated elements. In many cases they have provided the most efficient separations yet reported.

Tri- and hexa- fluoroacetylacetonates of most of the rare earth elements have been prepared (2). The normal acetylacetonates melt at about 160°, with both sublimation and decomposition, while the trifluoro- chelates melt at about 150° with sublimation, and those hexafluoro- complexes studied melt at about 140°C. with more rapid sublimation. However, in all cases, sublimation was very slight and separations based upon differences in vapor pressure were not attempted.

On the other hand, the results of Quill and co-workers, as yet incomplete, have shown that excellent separations of the rare earth elements can be made by fractional thermal or chemical decomposition of their fluoroacetylacetonates (8). Surprisingly large amounts of neodymium salts have been prepared in pure form using this separation method.

VanValkenburgh and Johnsen (9) have indicated that the fractional sublimation of mixtures of hafnium (IV) and zirconium (IV) 1,1,1-trifluoroacetylacetonates at 160° and 1.5 mm. pressure results in a marked separation of the two elements; the best yet reported over certain composition ranges. The vapor pressure of the hafnium compound is considerably greater than that of the corresponding zirconium chelate.

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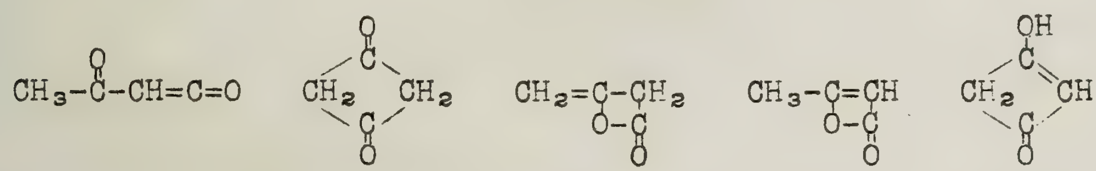
THE STRUCTURE OF ALDOKETENE DIMERS

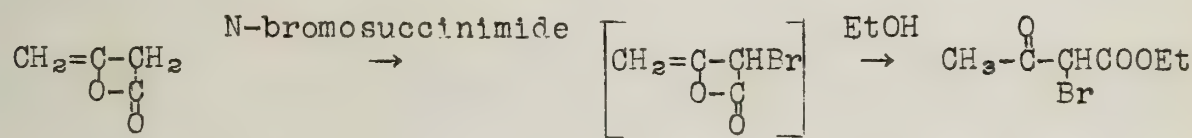
Reported by John C. Lorenz January 6, 1950

Ever since its first preparation by Chick and Wilsmore (1), the structure of diketene (and of all aldoketene dimers, since they have analogous physical and chemical properties) has been the subject of considerable research and debate. The chemistry of diketene and the evidence favoring the several postulated structures have been adequately summarized by Boese (2) and by Hanford and Sauer (3). The diketene structures that have been most seriously considered are shown below.



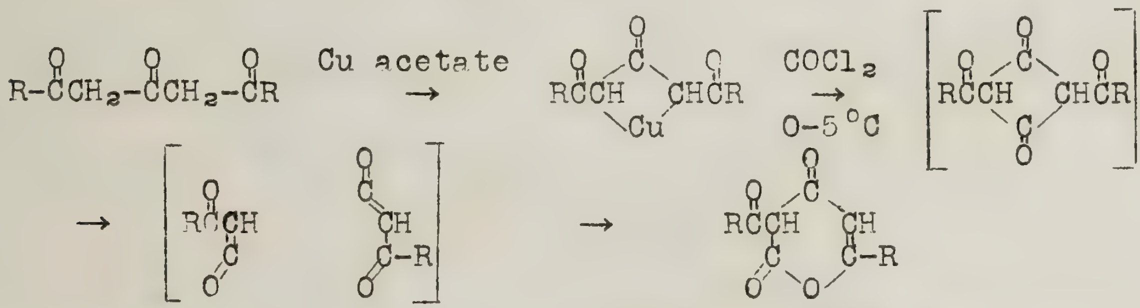
I II III IV V

Two recent reactions, although they may not be admitted as proof of any one structure, are of interest in this connection. The work of Blomquist (4) employing N-bromosuccinimide would favor structure III provided one assumes that this reagent preferentially brominates an allylic position.



No ethyl-γ-bromoacetoacetate, which would be the product postulated from structure IV, could be isolated from this reaction.

The products of a reaction intended to produce 2,4-diacyl-1,3-cyclobutanediones (5,6) are readily explained by postulating the existence - at least momentarily - of acyl ketenes.



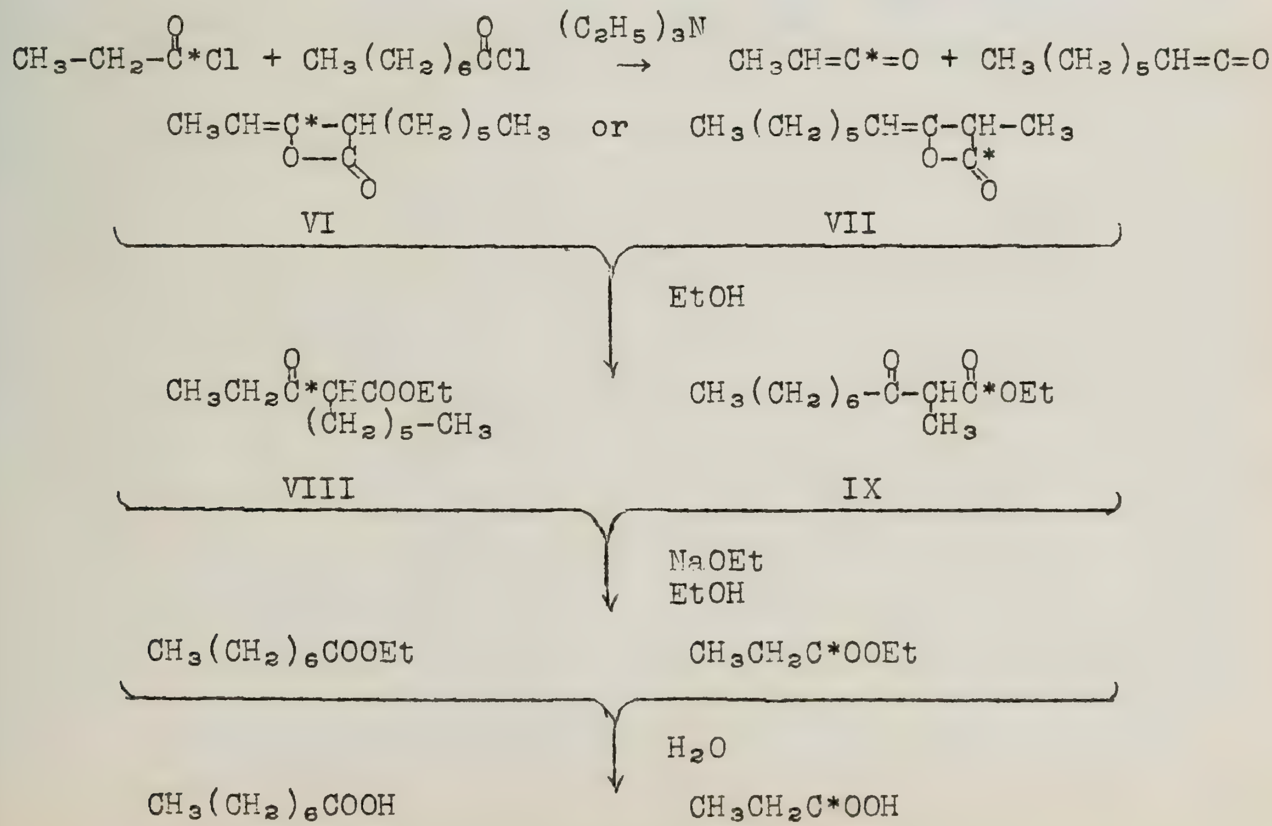
($R = CH_3$) Dehydracetic acid

$R = CH_3$ (5), CH_2CH_3 or $CH_2CH_2CH_3$ (6)

The infrared spectra studies of Miller and Koch (7), and the recent use of C^{14} by Roberts and Armstrong (8) present evidence more useful in evaluation of the nature of diketene.

Miller and Koch eliminated structures I and V because of the absence of the characteristic absorption frequencies corresponding to the C=C=O and O-H groupings, and proceeded to show that diketene was probably an equilibrium mixture of two (or more) forms. They based their conclusions on the observation of marked reversible variation in the infrared spectra with changes in temperature. If the substance were an equilibrium mixture, such changes would be expected from variations in the equilibrium constant according to the equation $d \ln K/dT = \Delta H/RT^2$. They did not completely eliminate structure II as a possible component of the mixture, but they considered it unlikely because of other chemical and physical evidence.

Roberts and Armstrong, by studying the reaction products of aldoketene dimers containing C^{14}, have eliminated structure II as a possible component of any equilibrium mixture that might exist. They prepared the mixed methyl-hexyl ketene dimer by the method of Wedekind (9) in which they used C^{14} carbonyl labeled propionyl chloride and unlabeled caproyl chloride. The mixed dimer was separated from methyl and hexyl ketene dimers by fractional distillation. The mixed dimer was subjected to the reactions shown.



Separate by fractional distillation

The activity of the caprylic acid was 1.5% of the activity per labeled carbon of the mixed dimer. Since the cyclobutane-1,3-dione structure (II) with its equivalent carbonyl groups would have been expected to produce equal activity in both caprylic and propionic acids, the <u>maximum</u> amount of mixed dimer that could have the structure II is 3%.

With the knowledge that practically none of the mixed dimer has the structure II it is possible to determine the relative amounts of forms VI and VII by radioactive analysis of the CO_2 formed by hydrolysis and decarboxylation of the mixture of esters VIII and IX. The CO_2 formed had 67% of the activity of the ester mixture so that the composition of the original mixed dimer must be 33% VI and 67% VII.

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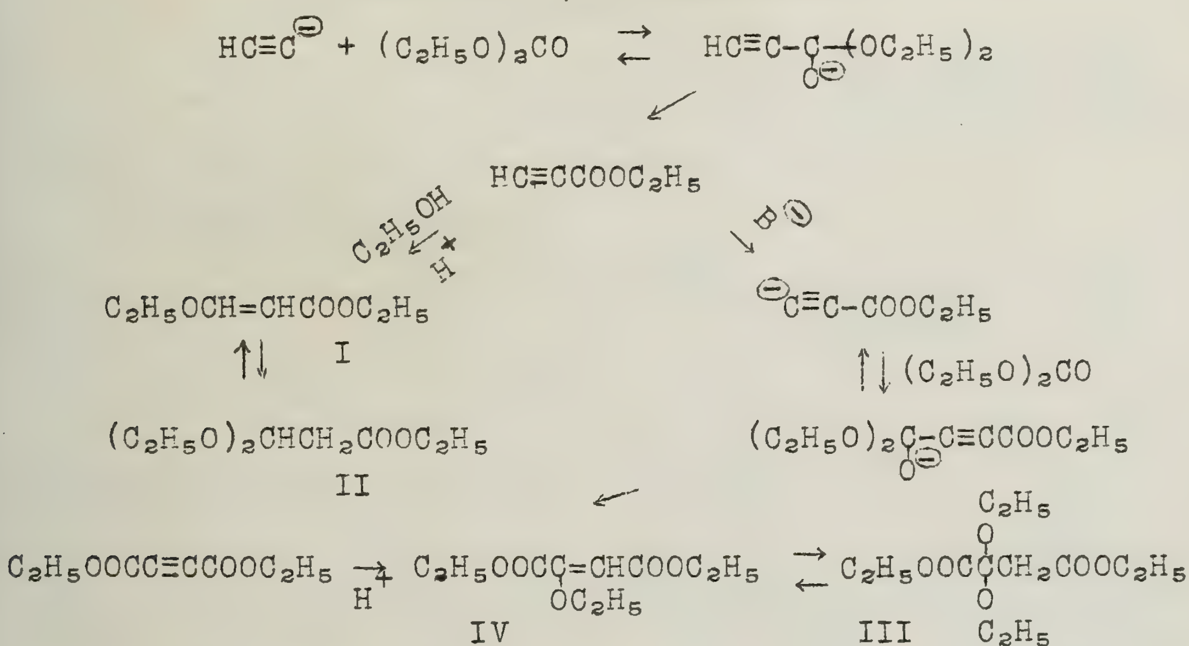
THE REACTION OF ACETYLENE WITH SOME ESTERS

Reported by Henry Z. Friedlander January 13, 1950

Four esters are formed when ethyl carbonate reacts with acetylene in the presence of a basic catalyst (3). The chief products are ethyl ethoxyacrylate (I) and ethyl β,β-diethoxypropionate (II). There are also a little ethyl α,α-diethoxysuccinate (III) and traces of ethyl ethoxymaleate (IV). The proposed course of the reaction is the attack of the polarized carbonyl group by the acetylide ion. This is a general reaction of 40-70% yield, getting better as the alkyl group increases in size.

$$HC\equiv CH + B^{\ominus} \rightleftarrows HC\equiv C^{\ominus} + BH$$



Exchange Reactions (5,10)

This reaction becomes more useful when the products are refluxed with any primary or secondary alcohol or mercaptan which boils above 78°. With bisulfate catalyst about 75% of the transetherification product was isolated. With the diacylated products III and IV the reaction proceeds only above 150°C with HSO_4^- and gives both transesterification and transetherification. With the BF_3·ether complex as catalyst only saturated exchange products result. 1,3 Dioxolanes and 1,3 dioxanes can be made by exchange with 1,2 or 1,3 glycols respectively. The yield is 80-95%.

Claisen Rearrangements (10)

When the above transetherification is done with allyl alcohol, the product is ethyl β-alloxyacrylate (V). This allyl vinyl ether rearranges to give ethyl α-formylallylacetate (VI).

$$\underset{\text{V}}{CH_2=CH-CH_2OCH=CHCOOC_2H_5} \xrightarrow[\text{(A or B)}]{\Delta} \underset{CH_2CH=CH_2}{OCH-CHCOOC_2H_5} \quad \text{VI}$$

The aldehyde ester exists in a keto-enol equilibrium with the enol form probably as a chelated ring.

A side reaction of the Claisen rearrangement which can be manipulated to become the main reaction is a reverse Claisen condensation of the α-formylester to produce unsaturated acetates (VII).

$$\underset{R}{OCHCHCOOR} \ \xrightarrow[ROH]{(RONa)} \ \underset{VII}{RCH_2COOR} + RCOOH$$

These same reactions with the dialkoxysuccinate (III) yield allyl allyloacetate and allyl oxalate.

An additional reaction of compound V is a simultaneous Claisen rearrangement and acylation with anhydrides to give ethyl β-acyloxy-α-allylacrylate (VIII). The latter reacts with alcohols to give alkyl β-alkoxy-α-allylacrylate (IX).

$$CH_2{=}CHCH_2OCH{=}CHCOOC_2H_5 \xrightarrow{(RCO)_2} RCOOCH{=}\underset{CH_2CH=CH_2}{C}COOC_2H_5 \quad VIII$$

$$RCOOCH{=}\underset{CH_2CH=CH_2}{C}COOC_2H_5 \xrightarrow[(A)]{R'OH} R'OCH{=}\underset{CH_2CH=CH_2}{C}COOR' \quad IX$$

<u>Condensation and Aromatization</u> (7,11,4)

The unsaturated alkoxy esters I and IV are Michael condensation acceptors and thus react with malonic and methyl malonic ester. Under forcing conditions the products are aromatic esters. Methyl malonic ester and ethyl ethoxyacrylate (I) give either ethyl α-methyl-β-ethoxyglutarate (X) or <u>trans</u> ethyl α-methyl-β-glutaconate (XI) depending on the relative amounts of the reactants used. Benzaltrimethylammonium ethoxide is the catalyst.

$$CH_3CH(COOC_2H_5)_2 + \underset{I}{C_2H_5OCH{=}CHCOOC_2H_5} \xrightarrow{(quat.)}$$

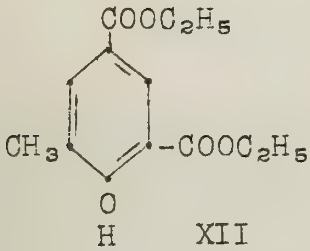
$$[CH_3C(COOC_2H_5)_2CH(OC_2H_5)CH_2COOC_2H_5] \rightleftarrows [CH_3C(COOC_2H_5)_2CH{=}CHCOOC_2H_5]$$

$$\downarrow \qquad\qquad\qquad\qquad \downarrow$$

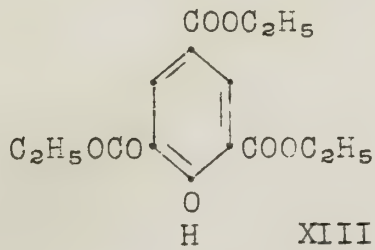
$$\underset{X}{CH_3CH(COOC_2H_5)CH(OC_2H_5)CH_2COOC_2H_5} \rightleftarrows \underset{XI}{CH_3CH(COOC_2H_5)CH{=}CHCOOC_2H_5}$$

With sodium ethoxide catalyst under severe conditions ethyl-4-hydroxy-5-methyl isophthalate (XII) is the main product. Under

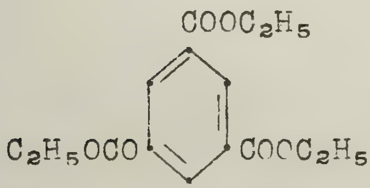
these conditions with malonic ester ethyl hydroxytrimesate (XIII) is isolated. But if benzaltrimethylammonium ethoxide catalyst is employed ethyl trimesate (XIV) is found whether or not malonic ester is present. Self-condensation of I with sodium ethoxide, however, yields ethyl 4-hydroxy-5-formylisophthalate (XV).



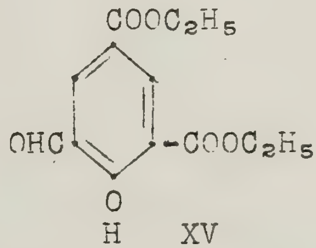
XII



XIII



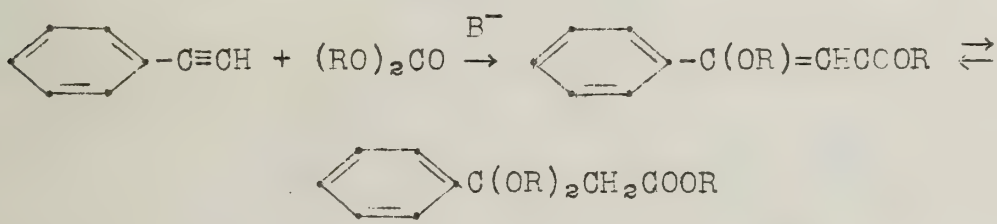
XIV



XV

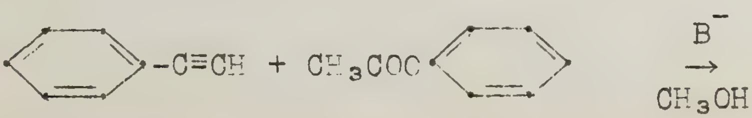
Substituted Acetylenes (2,4,7)

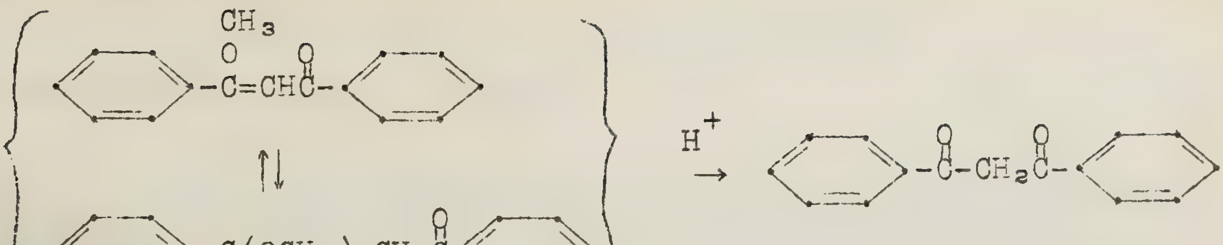
The monosubstituted acetylenes form alkoxyacrylates and acetals of β-ketoesters with alkyl carbonates in yields of 75-80%. Twice as much unsaturated ester is found. For example:



$$CH_2{=}\underset{CH_3}{C}{-}C{\equiv}CH + (RO)_2CO \xrightarrow{B^-} CH_2{=}\underset{CH_3}{C}{-}\underset{\underset{R}{O}}{C}{=}CHCOOR \rightleftarrows CH_2{=}\underset{CH_3}{C}C(OR)_2CH_2COOR$$

Methyl benzoate which also has no active α hydrogen atom has been employed as the acylating agent. Presumably pivalic ester would act analogously, but this has not been attempted. With acetylene the trimer cyclizes to give tribenzoylbenzene and with phenylacetylene dibenzoylmethane (XVI).





XVI

Phenylacetylide ion (1,8)

A rarity in organic chemistry is a different reaction of an organic anion with different cations. Lithium phenylacetylide yields tertiary carbinols with many esters, but sodium phenylacetylide stops at the ketone or gives intractable oils. Potassium acetylide only could be acetylated. In contrast to the unreactivity of potassium phenylacetylide is the work of Weizmann and coworkers, who found that the -O-C-O and -O-C-C-O- linkages activated acetylene-potassium hydroxide mixtures so that carbonyl groups are attacked. This makes it possible to make potassium acetylide with as much as 15% water present in place of older and more laborious anhydrous reactions using the metal in ammonia. This reaction complements the Reppe ethynylation which is satisfactory for aldehydes but not ketones. A representative reaction is:

$$CH_3COCH_3 + KOH + HC{\equiv}CH \xrightarrow{-O-C-O-} CH_3\underset{CH_3}{C}(OH){-}C{\equiv}CH \rightarrow CH_3\underset{CH_3}{\overset{OH}{C}}{-\!\!-}\underset{CH_3}{\overset{OH}{C}}{-}CH_3$$

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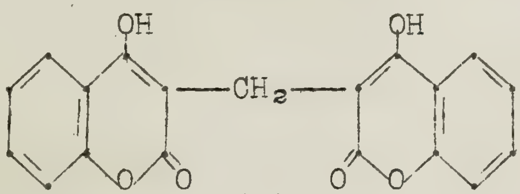
THE SYNTHESIS OF 4-HYDROXYCOUMARINS

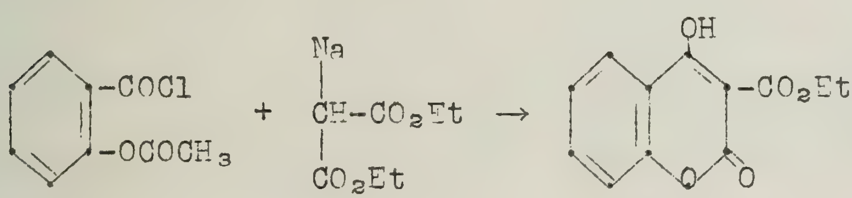
Reported by Charles F. Gilman   January 13, 1950

Interest in 4-hydroxycoumarins has been stimulated by the discovery that several naturally occurring substances (1,2), in particular dicumarol (I), which is the causative agent in the "sweet clover disease" in cattle (a disease which destroys the coagulatory powers of blood) belong to this class of compounds. Continued attention to the chemistry of 4-hydroxycoumarins is reflected in the announcement several weeks ago (3) that a new rodenticide, related to dicumarol, effectively kills rats without seriously endangering human or other animal life.



(I)

Anschutz (4) prepared 4-hydroxycoumarin (III) (benzotetronic acid) by condensing o-acetoxybenzoyl chloride with the sodio derivative of either acetoacetic or malonic ester, followed by deacetylation or decarboxylation of the 3-substituted-4-hydroxycoumarin (II).

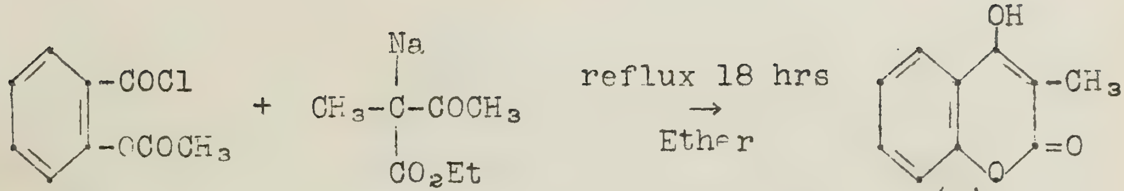


(II)

(III) R = H
(IV) R = C_2H_5

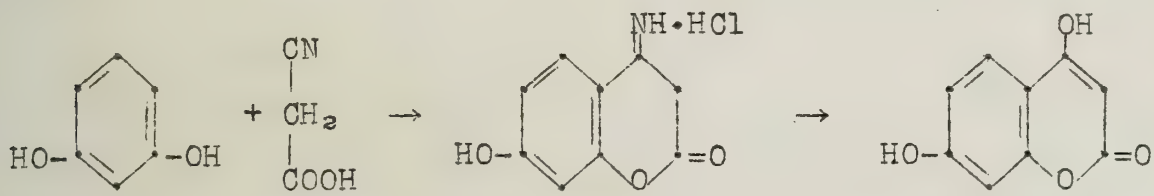
Although extension of this procedure to nuclear substituted salicylic acids enabled Anschutz and his students to prepare a large number of derivatives of III, they never succeeded in introducing a substituent in the 3-position of the molecule. In the hope of obtaining IV they attempted to condense ethyl malonic ester with o-acetoxybenzoyl chloride, but the operation was unsuccessful. Failure on the part of this investigator to synthesize a compound through a scheme calling for a 3-disubstituted-4-hydroxycoumarin as an intermediate is in agreement with the inability of later investigators to prepare any 4-hydroxycoumarins disubstituted in the 3-position.

Heilbron and Hill (6) modified the original procedure of Anschutz. Starting with o-acetoxybenzoyl chloride and the sodio derivative of methyl acetoacetic ester, they were able to obtain directly 3-methyl-4-hydroxycoumarin (V) in 60% yield, thereby realizing a condensation, a cyclization, and a deacetylation all in a single operation.

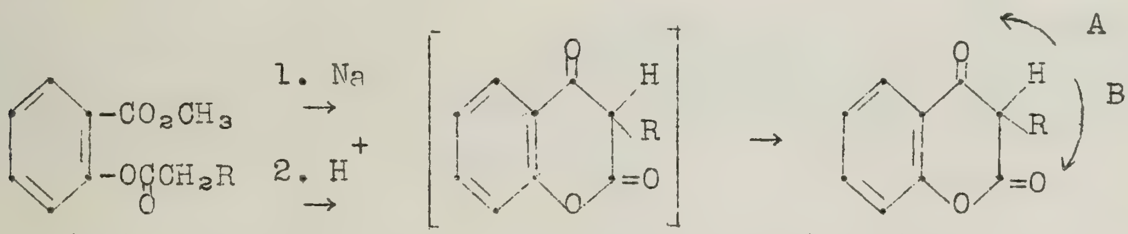


(V)

Sonn (7) and Bauer and Schoder (8) applied the Hoesch synthesis (9) to the preparation of 4-hydroxycoumarin having hydroxyl substituents on the benzene ring. By condensing cyanoacetic ester with resorcinol or phloroglucinol in the presence of hydrochloric acid and zinc chloride, followed by hydrolysis of the intermediate ketimide, the corresponding substituted 4-hydroxycoumarin was formed.

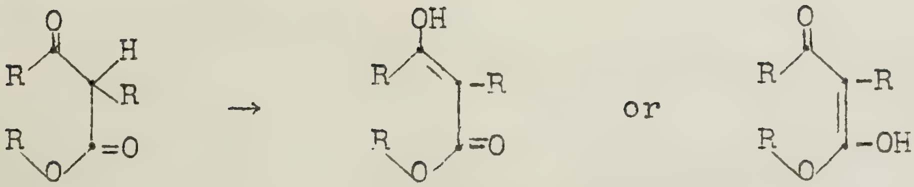


The method of Pauly and Lockemann (10) depends on an intramolecular Claisen condensation and consists in treating methyl-o-acyloxybenzoates (VI) with metallic sodium at elevated temperatures. Recently this reaction has been thoroughly investigated by Mentzer and his students in France (11) and by Link and his coworkers in this country (12). Both of these groups have demonstrated the general utility of the process and have employed it in the preparation of a number of compounds. This general synthesis can be represented by the following sequence in which R may be hydrogen, an alkyl, or an aryl residue.



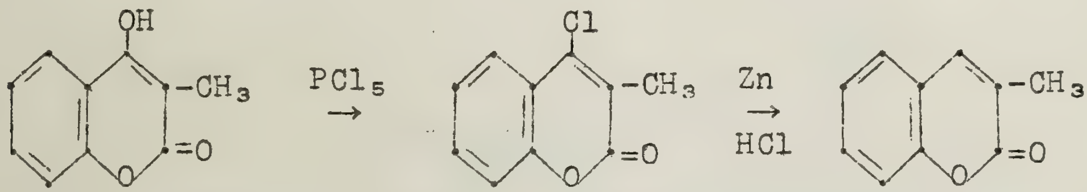
(VI) (VII) (VIII) A or B

The question as to whether enolization proceeds by route (VIII) A or (VIII) B was resolved by Mentzer largely on theoretical grounds (11). Of particular value to him in this connection was the treatise of Eistert (5), in which the various enolizable radicals are classified according to the strength with which they attract the neighboring hydrogen. According to this classification, the O=C-R group enolizes more readily than does the O=C-OR group; thus, a substance of form (IX) has the tendency to be converted into (IX) A rather than into (IX) B.



(IX) (IX) A (IX) B

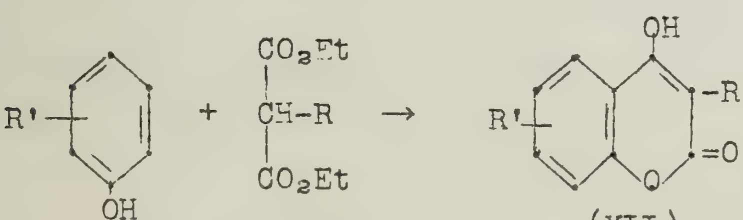
Corroborative evidence that this viewpoint is the correct one was obtained by the French worker in the particular case of 3-methyl-4-hydroxycoumarin. In order to replace the hydroxyl group by hydrogen he treated 3-methyl-4-hydroxycoumarin (X) with phosphorous pentachloride and reduced the chloro derivative so formed by zinc and hydrochloric acid to the known 3-methyl coumarin (XI).



(X) (XI)

Recognizing, however, that reagents such as phosphorous pentachloride are capable of causing migration of double bonds, Mentzer cautiously refrains from according to his work the status of an absolute proof. Recourse to physical methods of analysis, such as examination of absorption spectra, provided no significant information upon which to base a choice between the two possible structures.

Mentzer (13,14) undertook a systematic study of the action of malonic esters on phenols. Extension of this study to monosubstituted malonic esters resulted in the formation of the corresponding 4-hydroxycoumarins (XII) in yields considerably in excess of those obtainable by other methods.



(XII)

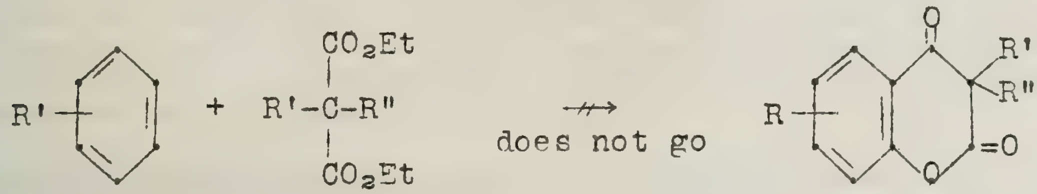
R' = H, Aryl or Alkyl

R = Aryl or Alkyl

Best results were obtained with phenols substituted in the meta position. In contrast, substituents in the ortho position proved to be of a deleterious nature, a fact which is readily explainable in terms of the steric hindrance which a substituent ortho to a phenolic group often exercises on this function. Since the hindrance caused by a methoxy group is recognized as being

more pronounced than that due to methyl, it is not surprising that 8-methyl-3-phenyl-4-hydroxycoumarin could be prepared, although in very low yield (10%), while the corresponding 8-methoxy-3-phenyl-4-hydroxycoumarin resisted all attempts at synthesis.

Despite numerous variations in experimental conditions, all attempts to prepare compounds of type XIII by the use of disubstituted malonic esters were uniformly unsuccessful, no compounds of this kind being as yet described.



(XIII)

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CHLORAMPHENICOL (CHLOROMYCETIN)
Structure Proof and Synthesis

Reported by Charles J. Strickler January 13, 1950

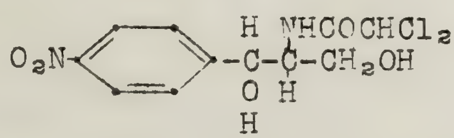
Introduction: The antibiotics have assumed a major role in the field of pharmaceuticals since the discovery of the bacteriostatic action of Penicillin. Chloromycetin is unique in that it is the first antibiotic to be produced synthetically on a commercial scale, and is probably the first naturally occurring compound known that contains a nitro group or which is a derivative of dichloroacetic acid. It shows marked bacteriostatic action against a number of Gram-negative organisms and chemotherapeutic activity against a number of Rickettsia species and at least one virus. Its low order of toxicity and suitability to oral administration promise extensive future use (1,2,4).

Isolation and Structure Proof: Chloromycetin was first isolated by research chemists of Park, Davis, and Company (3,5,6) from the filtrate of a submerged aerated culture of a Streptomyces species obtained from a soil sample of a mulched field near Caracas, Venezuela by P. R. Burkholder of Yale.

Chloromycetin is more stable than Penicillin or Streptomycin in acid solution, and unstable in dilute alkali. It is neutral, very slightly in soluble in water, insoluble in 5% sodium hydroxide, and soluble in many organic solvents. It can be sublimed in high vacuum without decomposition, is optically active ($[\alpha]_D^{25}$ + 19° in EtOH; -25.5° in EtOAc), and melts sharply at 150.1°. Elemental analysis showed C, H, N and non-ionic Cl. Its molecular weight (micro-Rast) was approximately 310 and the $E_{1\,cm}^{1\%}$ was 298 at 270 m . The empirical formula best satisfying analytical data was $C_{11}H_{12}Cl_2N_2O_5$. The position and shape of the ultraviolet maximum suggested a nitrobenzene derivative.

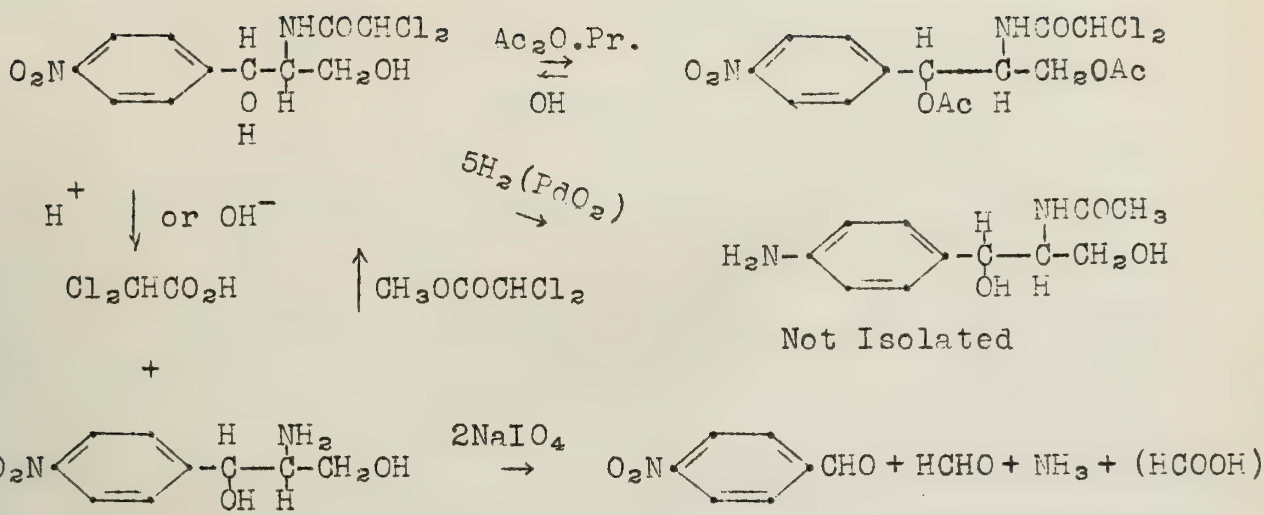
Chemical tests indicated no carbonyl function, no primary amino group, possibly an acetamido grouping, two hydroxyl groups, and a nitro group. The compound took up 5 molecular equivalents of hydrogen on reduction with palladium oxide catalyst and the resulting solution contained ionic halogen, showed presence of a base, and gave an ultraviolet spectrum similar to p-toluidine.

By these preliminary tests, and degradation studies (Table I) the structure of chloramphenicol was tentatively postulated (7) as:



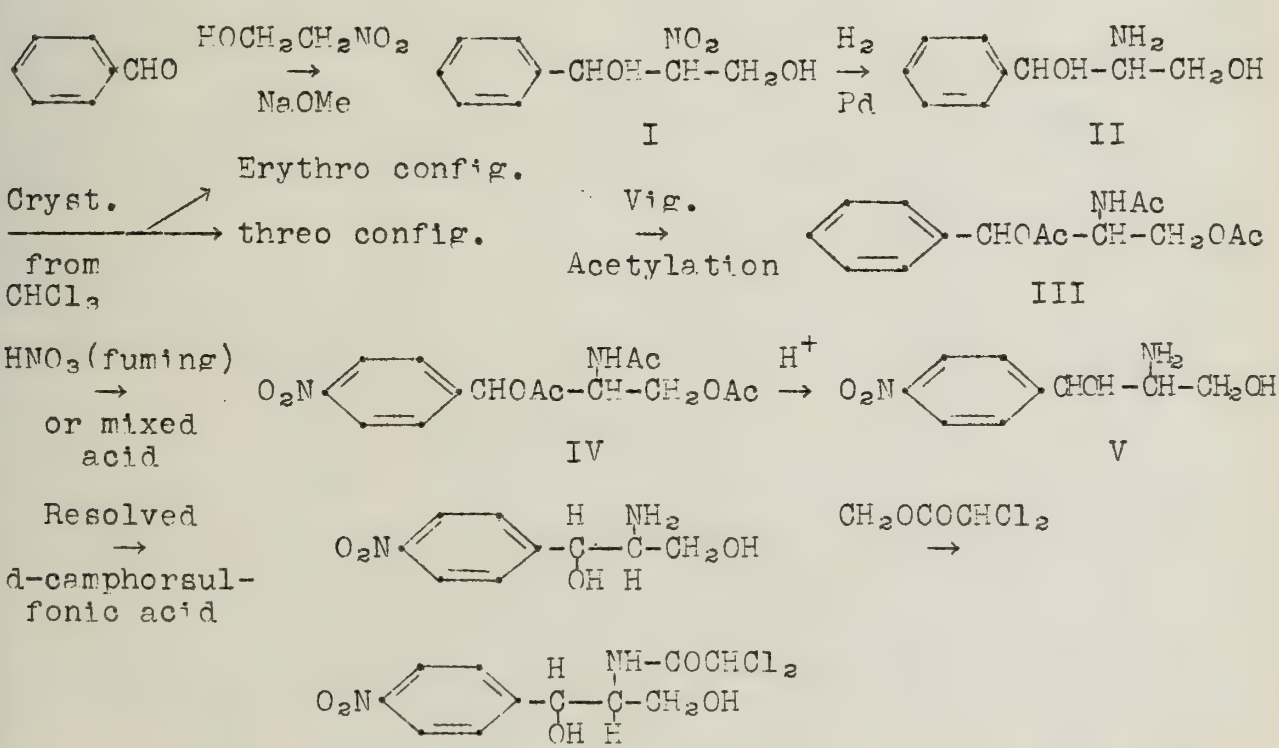
D-threo-N-(1,1'-dihydroxy-1-p-nitrophenylisopropyl)-dichloroacetamide. (Configuration of carbon atoms by comparison with Ephedra series and by considering the compound as a substituted glycerol.)

Table I



Synthesis: The final step of proof was the total synthesis of Chloromycetin and comparison with the natural product (8). This was first done by the series of reactions diagrammed in Table II. The erythro and threo configurations were differentiated by carrying them through complete synthesis and comparing with natural products.

Table II



The product melted at 150.5-151.5° and exhibited the same activity against Shigella paradysentariae as the natural product.

Two other syntheses (Tables III-IV) were then developed to make the process more suitable for large scale production (9,10). They were both aimed at more practical production of the free base (V Table II). Beyond this point all three are the same.

Table III

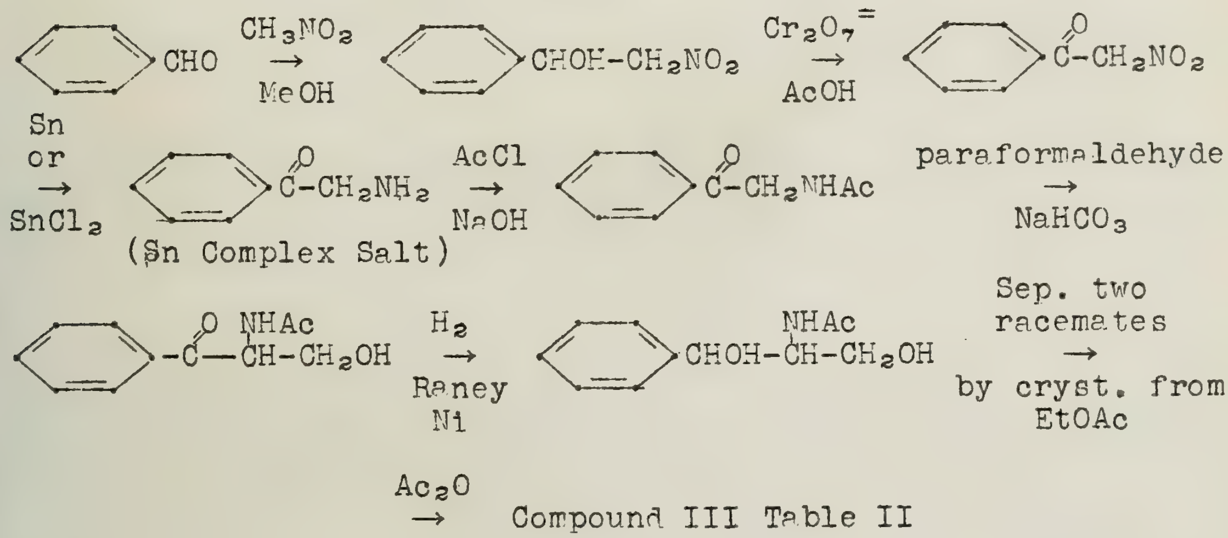
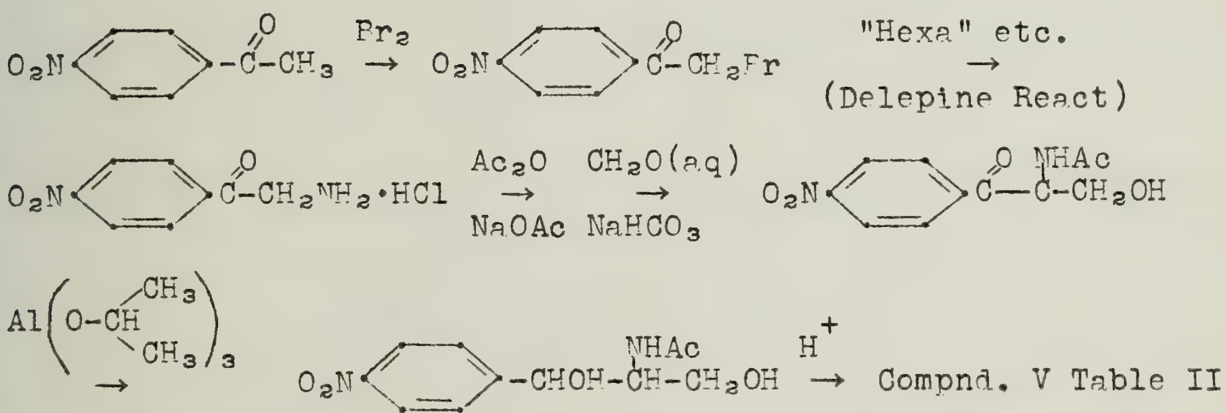


Table IV



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γ-ELIMINATION INVOLVING SILICON
A New Synthesis of the Cyclopropane Ring

Reported by Allan D. Gott January 20, 1950

Work has recently been done in synthesizing new organo-silicon compounds (2) and in studying the removal of silicon from organic compounds containing this element. Whitmore and corworkers studied the action of bases on removal of silicon from various compounds which contained halogen groups in positions alpha, beta and gamma to the terminal silicon.

Organo-silicon compounds with a chloro group in the α position, such as α-chloroethyl trichloro silane, are unattacked by base but with the chloro in the β-position, a cleavage of the carbon-silicon bond occurs (4). All examples found take place as:

$$\begin{matrix} Y_2C-Si\lessdot \\ Y_2C-X \end{matrix} \longrightarrow \begin{matrix} Y_2C \\ \| \\ Y_2C \end{matrix}$$

The mechanism of these reactions is similar to dehydrohalogenation of ordinary organic halides according to the following (4):

$$HO^- \dashrightarrow \overset{|}{\underset{/\,\backslash}{Si}}-CH_2-CH_2-Cl \longrightarrow \underset{/\,\backslash}{\overset{|}{Si}}OH + CH_2{=}CH_2 + Cl^-$$

Here silicon acts as an electronic sink and attracts the electron pair of the base. Among the effective reagents for causing β-elimination are alcoholic bases, aqueous alkali, water, potassium acetate in glacial acetic acid, methyl magnesium bromide, small amounts of aluminum chloride, silver nitrate in methanol, and in a few cases heat along will suffice (5).

γ-Halogen-silicon compounds could be converted into cyclopropane (1) with elimination of the silicon.

$$\begin{matrix} H_2C-Si\lessdot \\ H_2C \\ H_2C-X \end{matrix} \longrightarrow \begin{matrix} CH_2-CH_2 \\ \diagdown\ CH_2 \diagup \end{matrix}$$

γ-Eliminations of halogen to afford cyclic compounds are numerous in organic chemistry (6).

$$\begin{matrix} CH_2CH(CO_2Et)_2 \\ | \\ CH_2Br \end{matrix} \xrightarrow{NaOEt} \begin{matrix} CH_2 \diagdown \\ | \quad C(CO_2Et)_2 \\ CH_2 \diagup \end{matrix}$$

However this type of synthesis results only in cyclopropane derivatives and not in cyclopropane itself.

Freund first prepared cyclopropane in about 1882 (6) by the reaction of sodium on 1,3 dibromopropane. Hass (8) chlorinated propane to obtain a 19.3% yield of the 1,3-dibromo compound, which was separated by boiling point differences from other products. The dibromopropane was treated with magnesium and iodine as catalyst and a mixture of dibutyl ether and xylene as solvent. The evidence supported formation of an organo-metallic intermediate (8).

$$XCH_2CH_2CH_2X + Mg \rightarrow (XCH_2CH_2CH_2MgX) \rightarrow \underset{\diagdown CH_2 \diagup}{CH_2{-}CH_2} + MgX_2$$

γ-Bromo propyl trimethyl silane was synthesized by the sequence of reactions shown below (1). When warmed with a catalytic amount of aluminum chloride, a 92% yield of pure cyclopropane resulted. The other product of the reaction was shown to be trimethyl bromo silane (9,7). Treatment with sodium hydroxide in place of aluminum chloride gave no cyclopropane.

$$(CH_3)_3SiCH_2MgCl \xrightarrow{\underset{\diagdown O \diagup}{CH_2{-}CH_2}} (CH_3)_3SiCH_2CH_2CH_2OH \xrightarrow{PBr_3}$$

$$(CH_3)_3SiCH_2CH_2CH_2Br \xrightarrow{AlCl_3} \underset{\diagdown CH_2 \diagup}{CH_2{-}CH_2} + (CH_3)_3SiBr$$

γ-Chloro-propyl trichloro silane when heated with a solution of sodium hydroxide in aqueous ethanol gave pure cyclopropane but only in a 31% yeid. None was obtained when aluminum chloride was used in place of sodium hydroxide.

These reactions involve removal of an element more electropositive than carbon, such as silicon, hydrogen, or an active metal as shown by Pauling's electronegativity scale (10), together with an element more negative than carbon, and finally, both involve electron-release to carbon from an element more positive than carbon (1).

β-Eliminations involving silicon are base-catalyzed and take place by a mechanism involving nucleophilic attack on the silicon (4). The introduction of a single halogen on the silicon decreases the reaction rate tenfold (1). Thus a decrease in the electrophilic activity of the silicon, caused by replacement of methyl groups with halogens as in the reaction of γ-chloro-propyl trichloro silane (1), should result in a decrease in reaction velocity. The low yield of cyclopropane from this compound may be explained in this way. The following mechanism has been proposed:

$$HO^- + -\overset{|}{\underset{|}{Si}}-CH_2-CH_2-CH_2-Cl \rightleftarrows \overset{\delta^-}{HO}-\overset{|}{Si}-CH_2-CH_2-CH_2---\overset{\delta^-}{Cl} \rightarrow$$

$$HO-\overset{|}{\underset{|}{Si}}- + \underset{\diagdown CH_2 \diagup}{CH_2{-}CH_2} + Cl^-$$

This mechanism is similar to 1:3 elimination of HX as proposed by Hauser (11).

$$B^- + H-C-C-C-X \rightleftarrows \overset{\delta^-}{B}---H---C-C-C---\overset{\delta^-}{X} \rightarrow BH + \underset{\diagdown C \diagup}{C{-}C} + X^-$$

The hydrogen is removed as a proton, the halo group is released with a complete octet of electrons and the molecule is stabilized by a shift of electron bonds. These may occur entirely or partially simultaneously (11).

The elctropositive nature of silicon and the ability of $AlCl_3$ to cause ionization of the carbon-halogen bond make a similar mechanism plausible in the reaction of γ-bromo propyl trimethyl silane with $AlCl_3$ to give cyclopropane (1):

$$-\overset{|}{\underset{|}{Si}}CH_2CH_2CH_2Br \xrightarrow{AlX_3} -\overset{|}{\underset{|}{Si}}CH_2CH_2\overset{+}{CH_2} + AlX_4^-$$

$$-\overset{|}{\underset{|}{Si}}CH_2CH_2\overset{+}{CH_2} \xrightarrow{AlX_4^-} -\overset{|}{\underset{|}{Si}}-X + \underset{\diagdown CH_2 \diagup}{CH_2-CH_2} + AlX_3$$

There are two possible reaction paths (1) for the silicon which are possible extremes of mechanism. (a) A transition state in which the siliconium ion is transferred to the new linkage with halogen without being set free.

$$-\overset{|}{\underset{|}{Si}}-CH_2-CH_2-\overset{+}{CH_2} + AlX_4^- \rightleftarrows \overset{\delta^-}{AlX_4}---\overset{|}{\underset{/\,\backslash}{Si}}--CH_2-CH_2-\overset{+}{CH_2} \rightarrow$$

$$AlX_3 + -\overset{|}{\underset{|}{Si}}-X + \underset{\diagdown CH_2 \diagup}{CH_2-CH_2}$$

(b) A reaction process in which a siliconium ion is actually set free prior to combination with halogen from AlX_4^-.

$$-\overset{|}{\underset{|}{Si}}-CH_2-CH_2-\overset{+}{CH_2} \rightleftarrows -\overset{\delta^+}{\underset{|}{Si}}--CH_2-CH_2-\overset{\delta^+}{CH_2} \rightarrow \underset{\diagdown CH_2 \diagup}{CH_2-CH_2} + -\overset{|}{\underset{|}{Si}}^+$$

$$-\overset{|}{\underset{|}{Si}}^+ \xrightarrow{AlX_4^-} -\overset{|}{\underset{|}{Si}}-X + AlX_3$$

In the mechanism applied to β-elimination the same question can be raised. Hydrolysis of triphenyl silyl fluoride in 50% water and 50% acetone does not take place with a siliconium ion intermediate with a positive charge on the silicon analagous to the carbonium ion (12). An intermediate with pentacovalent silicon seems more likely (12).

$$\underset{H}{\overset{H}{>}}\overset{\delta^+}{O}-\overset{C_6H_5}{\underset{C_6H_5\ \ C_6H_5}{Si}}-\overset{\delta^-}{F}$$

That silicon can react so is evidenced by the very stable $SiF_6^=$ ion. Although the existence of siliconium ions is unlikely with relatively weak electrophilic reagents such as the water-acetone mixture, it is still possible that siliconium ions may exist in the presence of exceptionally strong electrophilic reagents such as aluminum chloride (12).

Attempts have also been made to close larger rings using this method (1). 5-Bromopentyl trimethyl silane was prepared from γ-bromopropyl trimethyl silane by the action of magnesium followed by ethylene oxide and replacement of the hydroxyl with bromine. Treatment with aluminum chloride (3) resulted in a mixture of polymeric products and a low yield of impure pentene-1 (1). No

cyclopentane resulted. The electron deficiency on the carbon is too distant from the bromo group in the 5-position for an intramolecular transmission of charge sufficient for cyclization, in spite of the lesser strain involved in the formation of a 5-membered ring (1).

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RECENT STUDIES ON THE FREE RADICAL REACTIONS OF GRIGNARD REAGENTS WITH ORGANIC HALIDES

Reported by Franklin E. Mange January 20, 1950

Through the use of catalytic amounts of certain metal salts or through the use of certain Grignard reagents which can dissociate into free radicals, certain "anomalous" reactions of Grignard reagents may take place. The earlier work of M. S. Kharasch in this field has been reviewed (1).

Kharasch (2) has postulated a free radical mechanism to account for the various products obtained when a Grignard reagent reacts with an organic halide in the presence of a metal salt, the most effective of which is cobaltous chloride. The mechanism may be generalized as follows:

(a) $RMgX + CoCl_2 \rightarrow RCoCl + MgXCl$

(b) $2RCoCl \rightarrow R\text{-}R \quad 2CoCl\cdot$

(c) $R'X + \cdot CoCl \rightarrow R'\cdot + CoClX$

The cobaltous chloride is reduced to cobaltous subchloride ($CoCl\cdot$) by the Grignard reagent and the subchloride is then oxidized by the organic halide, and thus the subchloride acts as the chain carrier.

When R is aryl (2) the R radical forms biaryls exclusively. This seems to indicate that an aryl free radical is not formed in equation (b) for if such was the case, it would disproportionate forming higher polyaryls. The true nature of equation (b) is not fully known. Little work has been done in the case where R is alkyl (3), but from the data obtained, Kharasch believes that an alkyl free radical is generated in equation (b) rather than forming bialkyls. These free radicals would then react as explained below.

The fate of the R' free radical formed in equation (c) depends to some extent upon its electronegativity (4). If it is weakly electronegative (benzyl, etc.) it dimerizes, if it is of intermediate electronegativity (cyclohexyl, higher alkyl, etc.) it dimerizes and disproportionates, and if it is of higher electronegativity (aryl, lower alkyls, etc.) it disproportionates. Some free radicals notably the methyl radical attack the solvent (ether). In the case of the methyl free radical (5), methane is formed by the extraction of hydrogen from the ether molecule, and ethane and ethylene are formed in equal amounts by the rupturing of the carbon oxygen bond in the ether molecule followed by disproportionation of the ethyl free radical which is formed. In addition, rearrangement (4) of the free radical formed in equation (c) has been observed in a few cases.

Using the above generalities, Kharasch (4) was able to explain the formation of the various products when β,β-dimethylphenethyl chloride (I) was reacted with phenylmagnesium bromide in the presence of a catalytic amount of cobaltous chloride by the following mechanism.

(a) $C_6H_5MgBr + CoCl_2 \rightarrow C_6H_5CoCl + MgBrCl$

(b) $2C_6H_5CoCl \rightarrow C_6H_5{-}C_6H_5 + 2CoCl\cdot$

(c) $C_6H_5C(CH_3)_2CH_2Cl$ (I) $+ CoCl\cdot \rightarrow C_6H_5C(CH_3)_2CH_2\cdot + CoCl_2$

(d) $C_6H_5C(CH_3)_2CH_2\cdot \xrightarrow{\text{ether}} C_6H_5C(CH_3)_3$

(e) $C_6H_5C(CH_3)_2CH_2\cdot \xrightarrow{\text{rearrangement}} C_6H_5CH_2\dot{C}(CH_3)_2$

(f) $C_6H_5C(CH_3)_2CH_2\cdot \xrightarrow{\text{rearrangement}} C_6H_5\dot{C}(CH_3)CH_2CH_3$

(g) $C_6H_5CH_2\dot{C}(CH_3)_2 \rightarrow C_6H_5CH_2C(CH_3)=CH_3 + C_6H_5CH_2CH(CH_3)_2$

(h) $C_6H_5CH_2\dot{C}(CH_3)_2 \rightarrow C_6H_5CH=C(CH_3)_2 + C_6H_5CH_2CH(CH_3)_2$

The products obtained from this reaction are t-butylbenzene from equation (d), isobutylbenzene from equations (g) and (h), 2-methyl-3-phenylpropene from equation (g), β β-dimethylstyrene from equation (h), a mixture of dimers obtained by the combinations of the free radicals formed in equations (c), (e) and (f), and biphenyl from equation (b). Although no disproportionation products of the free radical formed in equation (f) could be isolated, this free radical might still have been formed and then dimerized exclusively. This seems reasonable in view of the fact that it is a radical of weak electronegativity.

Kharasch (6) was able to apply this type of reaction to develop a new synthesis of hexestrol dimethylether (II) by coupling anesthrol hydrobromide (III) in the presence of phenylmagnesium bromide and cobaltous chloride as follows:

$C_6H_5MgBr + CoCl_2 \rightarrow C_6H_5CoCl + MgBrCl$

$2C_6H_5CoCl \rightarrow C_6H_5{-}C_6H_5 + 2CoCl\cdot$

p-$CH_3OC_6H_4CHBrCH_2CH_3$ (III) $+ CoCl\cdot \rightarrow$ p-$CH_3OC_6H_4\dot{C}HCH_2CH_3 + CoClBr$

2p-$CH_3OC_6H_4\dot{C}HCH_2CH_3 \rightarrow$ (p-$CH_3OC_6H_4CH(C_2H_5)-)_2$ (II)

In many cases (7) an interchange of radicals seems to occur in the reaction of Grignard reagents and organic halides in the presence of metal halides. For example, when bromobenzene is treated with carbon dioxide after it is allowed to stand at 0° in the presence of butylmagnesium bromide and cobaltous bromide for ten minutes some benzoic acid is obtained. This indicates that some phenylmagnesium bromide must have been formed. Kharasch explains this result by the following postulated mechanism.

$$C_4H_9MgBr + CoBr_2 \rightarrow C_4H_9CoBr + MgBr_2$$

$$C_4H_9CoBr \rightarrow \cdot CoBr + C_4H_9\cdot$$

$$C_4H_9\cdot \rightarrow C_4H_{10} + C_4H_8$$

$$C_6H_5Br + CoBr\cdot \rightarrow CoBr_2 + C_6H_5\cdot$$

$$C_6H_5\cdot \rightarrow \text{polyphenyls and tar}$$

$$C_6H_5\cdot + C_4H_9MgBr \rightarrow C_6H_5MgBr + C_4H_9\cdot$$

The phenylmagnesium bromide then reacts to form biphenyl in the usual manner. Such interchanges are even more pronounced in the case of the lithium Grignards (8).

It is possible to utilize the free radicals generated by means of the catalyzed Grignard reactions to attack certain alkylbenzenes (9). For example, a substituted bibenzyl was prepared by the interaction of methylmagnesium bromide, methyl bromide, isopropylbenzene and a small amount of cobaltous chloride in a minimum amount of ether. This reaction may be represented by the following mechanism.

$$CH_3MgBr + CoCl_2 \rightarrow CH_3CoCl + MgBrCl$$

$$CH_3CoCl \rightarrow CH_3\cdot + CoCl\cdot$$

$$CH_3Br + CoCl\cdot \rightarrow CH_3\cdot + CoBrCl$$

$$C_6H_5CH(CH_3)_2 + CH_3\cdot \rightarrow CH_4 + C_6H_5\underset{\bullet}{C}(CH_3)_2$$

$$2C_6H_5\underset{\bullet}{C}(CH_3)_2 \rightarrow C_6H_5C(CH_3)_2C(CH_3)_2C_6H_5$$

$$CH_3\cdot + \text{ether} \rightarrow \text{gaseous products } (CH_4 + C_2H_6 + C_2H_4)$$

Although the yields were not good, they were improved by using the propyl radical, which has less tendency to attack ether. In some cases fair yields were also obtained by using higher temperatures without the use of a catalyst (9). For example, the reaction of ethylmagnesium bromide, ethyl bromide and isopropylbenzene may proceed by the following mechanism.

$$C_2H_5MgBr \rightarrow C_2H_5\cdot + \cdot MgBr$$

$$C_2H_5Br + \cdot MgBr \rightarrow C_2H_5\cdot + MgBr_2$$

$$C_6H_5CH(CH_3)_2 + C_2H_5\cdot \rightarrow C_2H_6 + C_6H_5\underset{\bullet}{C}(CH_3)_2$$

$$2C_6H_5\underset{\bullet}{C}(CH_3)_2 \rightarrow C_6H_5C(CH_3)_2C(CH_3)_2C_6H_5$$

$$2C_2H_5\cdot + \text{ether} \rightarrow \text{gaseous products } (C_2H_6 + C_2H_4)$$

Recently Wilds and McCormack (10) have modified the mechanisms employed by Kharasch. They believe that activated cobalt in the colloidal state is the chain carrier rather than cobaltous subchloride. Thus, for example, the reaction of ethyl magnesium bromide with anesthrol hydrobromide (III) in the presence of cobaltous chloride takes on the appearance of a Wurtz reaction.

$$2C_2H_5MgBr + CoCl_2 \rightarrow MgBr_2 + MgCl_2 + C_2H_5CoC_2H_5$$

$$C_2H_5CoC_2H_5 \rightarrow C_2H_6 + C_2H_4 + Co$$

$$2\underline{p}\text{-}CH_3OC_6H_4CHBrCH_2CH_3 \text{ (III)} + Co \rightarrow 2\underline{p}\text{-}CH_3OC_6H_4\underset{\cdot}{C}HCH_2CH_3 + CoBr_2$$

$$2\underline{p}\text{-}CH_3OC_6H_4\underset{\cdot}{C}HCH_2CH_3 \rightarrow \underline{p}\text{-}CH_3OC_6H_4CH(C_2H_5)CH(C_2H_5)C_6H_4OCH_3$$

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REACTIONS OF TERTIARY ACID CHLORIDES WITH AROMATIC COMPOUNDS

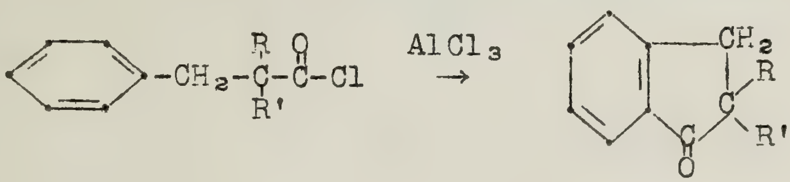
Reported by Victor Tullio January 20, 1950

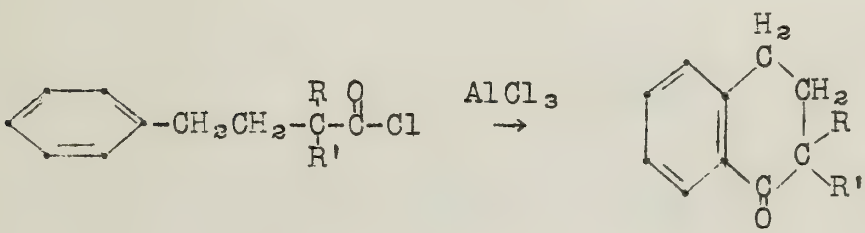
In their investigation of the Friedel-Crafts reaction using acid chlorides or anhydrides, Rothstein and Saboor (1) in 1934 found that the acid derivatives fell into two classes. The first includes the primary and secondary acid halides which yielded only ketones RCH_2COAr and $R_2CHCOAr$. The tertiary acid halides represent the second class and were found to form hydrocarbons with the loss of carbon monoxide.

$$R_3CCOX + ArH \xrightarrow{AlCl_3} R_3CAr + CO + HX$$

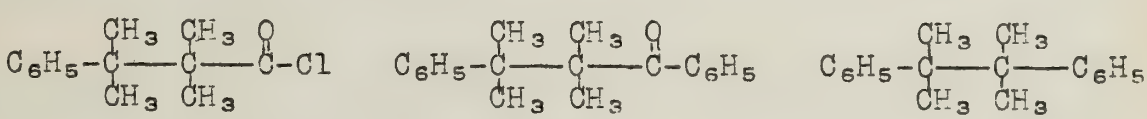
In recent papers, Rothstein and Saville (2,3,4,5,6) have undertaken a more extensive survey of the Friedel-Crafts reactions of the tertiary acid halides, which has resulted in some modification of the earlier ideas.

They found that, although tertiary acid halides usually produce hydrocarbons with elimination of carbon monoxide, ketone formation can occur. For example, when the following types of acid chlorides were used, cyclic ketones were formed exclusively.





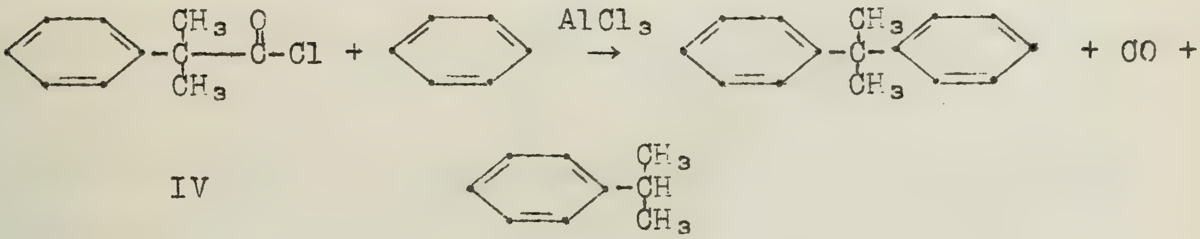
When Haller and Bauer (7) reacted I with $AlCl_3$ in a benzene solvent, only cyclization occurred and neither II nor III could be isolated.



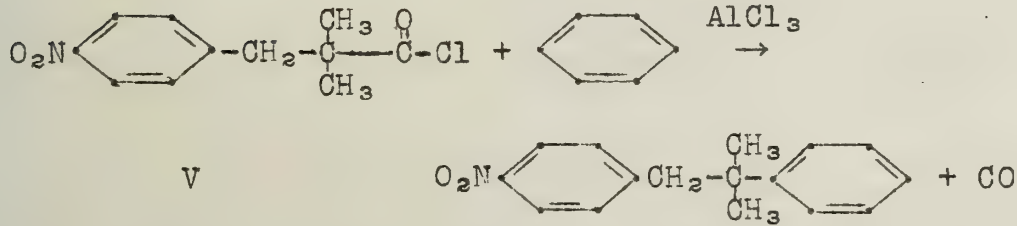
I II III

This indicates that cyclization is preferred over linear ketone formation or elimination of carbon monoxide. This is due in part to the ease of formation of five and six membered rings, and in part to the activation of the ring by the side chain itself.

If ring formation is hindered by shortening the side chain, as in IV, or if the benzene ring is deactivated, as in V, alkylation and no acylation occurs.



IV



V

The type of product formed in a Friedel-Crafts reaction sometimes depends on the nature of the aromatic component. Thus, oxalyl chloride produces benzophenone with benzene (8), but yields substituted benzils with anisole (9) and other phenolic ethers (10,11).

$$Cl-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-Cl \xrightarrow[AlCl_3]{C_6H_6} C_6H_5COC_6H_5 + CO + 2HCl$$

$$Cl-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-Cl \xrightarrow[C_6H_5OCH_3]{AlCl_3} CH_3OC_6H_4COCOC_6H_4OCH_3 + 2HCl$$

Rothstein and Saville (3) found that all of the tertiary acid chlorides they examined also yielded the corresponding ketone when treated with anisole instead of eliminating carbon monoxide as they do with benzene.

$$C_6H_5-C(CH_3)_2-COCl + C_6H_5OCH_3 \xrightarrow[\text{in ligroin}]{AlCl_3} C_6H_5-C(CH_3)_2-COC_6H_4OCH_3 \quad 71\%$$

$$\underset{\text{VI}}{(CH_3)_3CCOCl} + C_6H_5OCH_3 \xrightarrow[\text{in ligroin}]{AlCl_3} (CH_3)_3CCOC_6H_4OCH_3 \quad 80\%$$

The amount of $AlCl_3$ used varies with the type of product obtained. Thus, when pivaloyl chloride, VI, reacts with benzene to form t-butylbenzene, only catalytic amounts of $AlCl_3$ are required, although the reaction proceeds faster with more than this amount. When pivaloyl chloride forms t-butyl p-methoxyphenyl ketone with anisole, more than a mole of $AlCl_3$ is required.

When toluene or ethylbenzene in CS_2 is used instead of benzene or anisole with pivaloyl chloride, equal amounts of hydrocarbon and ketone are formed. With t-butylbenzene, only hydrocarbon is formed with pivaloyl chloride.

The first step in the reactions of the tertiary acid chlorides is considered to be the same as that which takes place in Friedel-Crafts reactions of all acid halides or anhydrides.

$$R_3C-\overset{O}{\overset{\|}{C}}-Cl + AlCl_3 \rightarrow R_3C-\overset{O}{\overset{\|}{C}}-Cl:AlCl_3 \rightarrow R_3C-\overset{O}{\overset{\|}{C}}\oplus + [AlCl_4]^{\ominus}$$

If a sufficiently active benzene ring is present, such as in anisole, the carbonium ion will react immediately with it to form a ketone. However, in the absence of an activated benzene ring, the carbonium ion may lose carbon monoxide to form a new and more stable carbonium ion.

$$R_3C-\overset{O}{\overset{\|}{C}}\oplus \rightarrow CO + R_3C\oplus$$

The new ion would then react with the unactivated benzene ring to form a hydrocarbon.

The prerequisite for the elimination of carbon monoxide is the electron releasing power of the R groups attached in $R_3CCO\oplus$. When R is alkyl, the elimination of CO is fairly rapid; but, if it is halogen, the speed of decomposition is reduced considerably. In fact, in trichloroacetyl chloride we have a rare example of a tertiary acid halide giving a ketone with benzene.

$$Cl_3C-COCl + C_6H_6 \xrightarrow{AlCl_3} Cl_3C-COC_6H_5$$

It is most unusual for a primary or secondary acid halide to produce a hydrocarbon with the loss of CO. However, with VII this does happen, although with VIII the normally expected ketone is obtained.

$$\underset{\text{VII}}{(p\text{-}CH_3C_6H_4)_2{>}CH-COCl} \qquad \underset{\text{VIII}}{(C_6H_5)_2{>}CH-COCl}$$

It would seem that the phenyl groups are not electron releasing enough to facilitate loss of CO, while the p-tolyl groups do possess this property.

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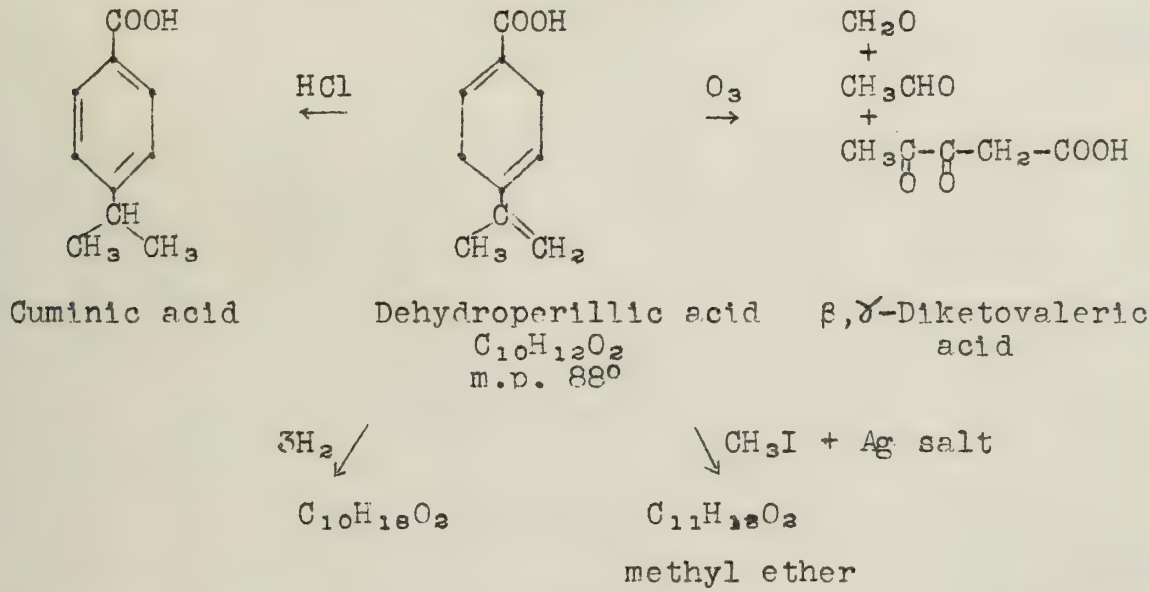
ANTIBIOTICS FROM THE HEARTWOOD OF THE WESTERN RED CEDAR

Reported by K. R. Eilar February 17, 1950

The durability of the wood of the Western Red Cedar (<u>thuja plicata</u>) has been found to be due to fungicidal compounds present in the Cedar heartwood. Aqueous extracts of the heartwood are very toxic to fungi and bacteria (1,2).

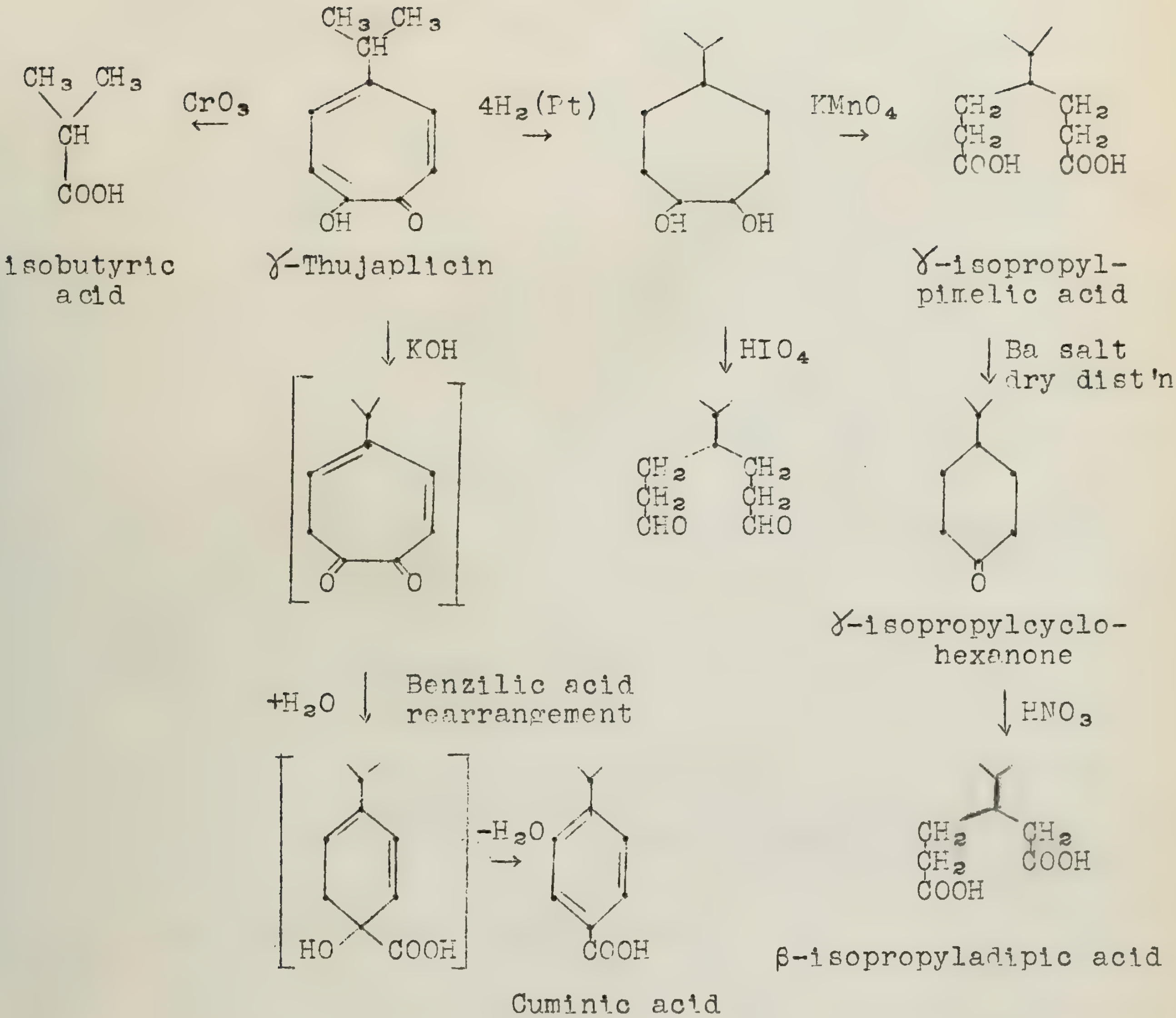
The first compound to be isolated from the Cedar heartwood and identified was dehydroperillic acid, whose structure was proven by the following reactions (3):



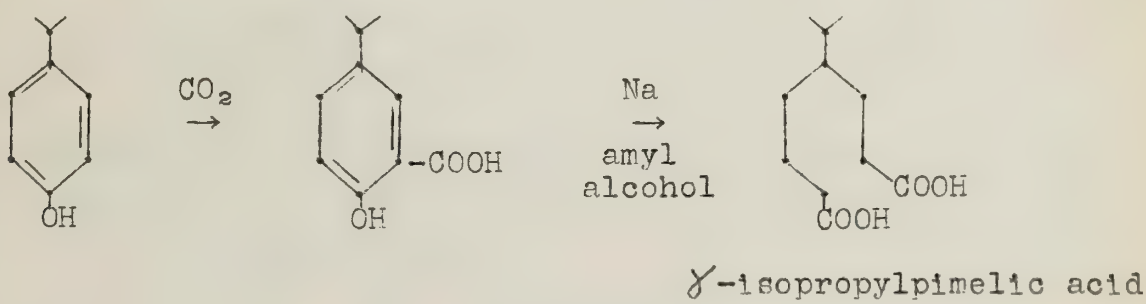
Pure dehydroperillic acid, however, had very low fungicidal activity.

The highly fungicidal and bactericidal components were identified as the three isomeric isopropyl cycloheptatrienolones, α, β, and γ-thujaplicin. These compounds have very similar ultra violet absorption spectra, they all give a green color with ferric chloride, a yellow alkaline solution, and a green copper complex with copper acetate; they are all acidic; they do not react with carbonyl reagents; they react with bromine giving crystalline bromo derivatives with evolution of hydrogen bromide; and they couple with diazotized amines to give red products (4).

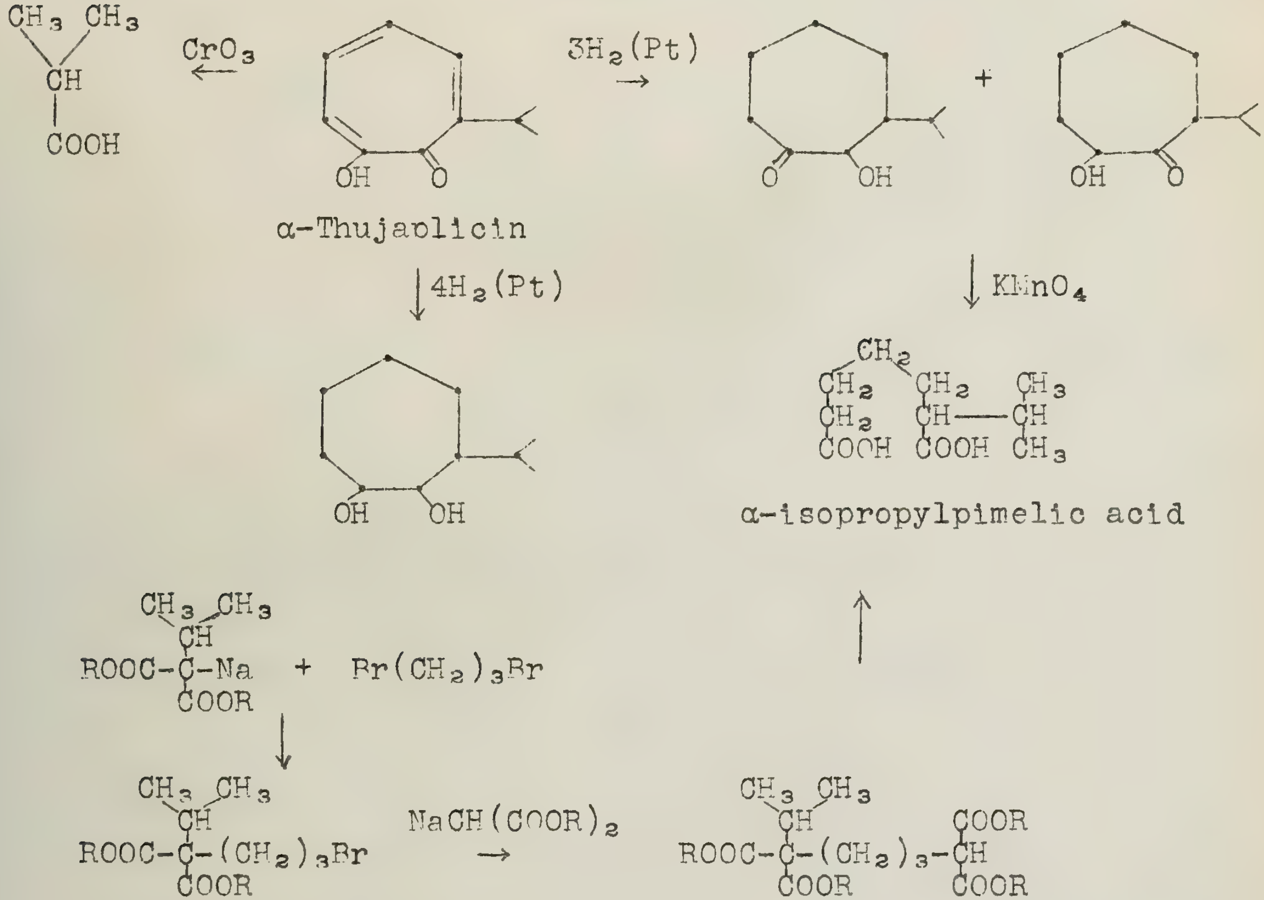
γ-Thujaplicin was shown to be γ-isopropyl cycloheptatrienolone by the following reactions (5):



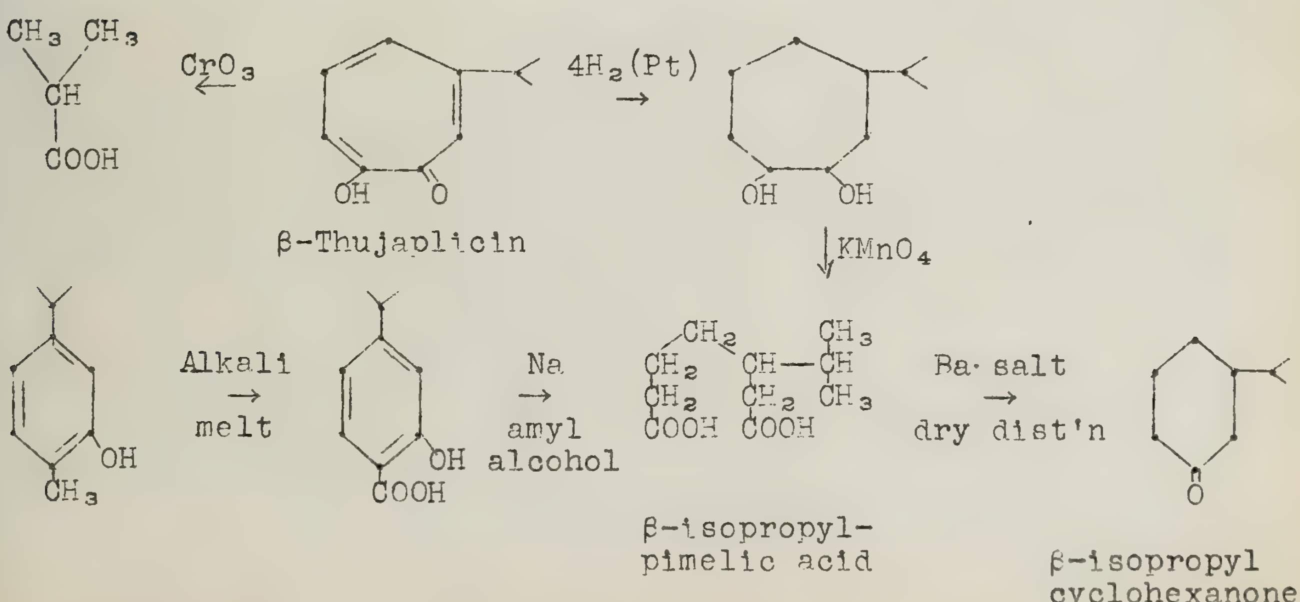
γ-Isopropylpimelic acid was synthesized by the following method:



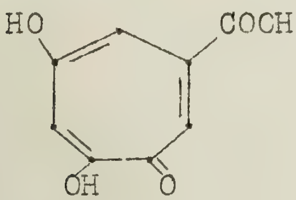
α-Thujaplicin was similarly found to be the α isomer (6):



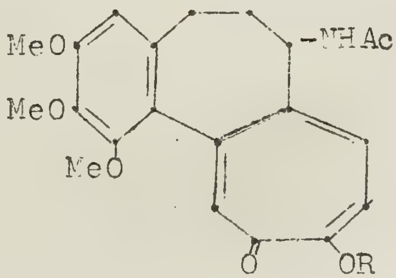
β-Thujaplicin is the β isomer (7):



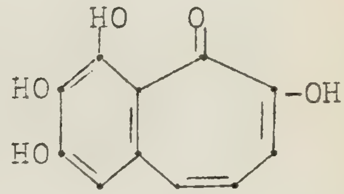
The cycloheptatrienolone system, for which Dewar proposes the term "tropolone" (8) has also been found in other natural products (8,9,10,11):



Stipitatic acid
(8)

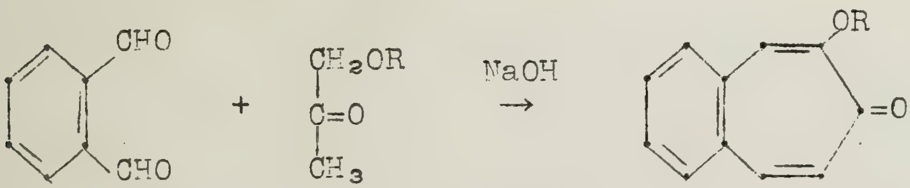


R=H: Colchiceine
R=Me: Colchicine
(9,10)



Purpurogallin
(11)

4,5-Benztropolone and two of its phenyl ethers have very recently been synthesized by Tarbell and coworkers in connection with their colchicine studies (12):



R = H: 4,5-Benztropolone
R = C_6H_5: phenyl ether of 4,5-benztropolone
R = p-$C_6H_4NO_2$: p-nitrophenyl ether

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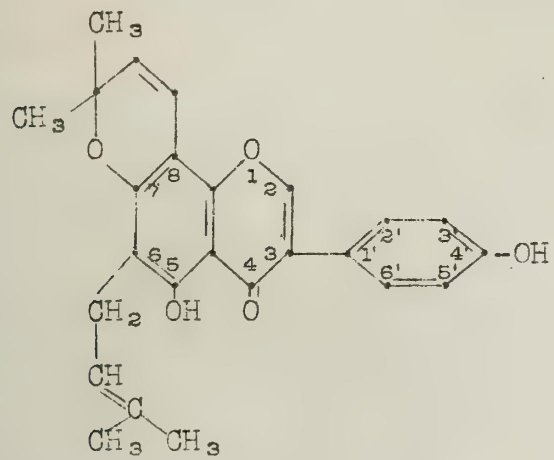
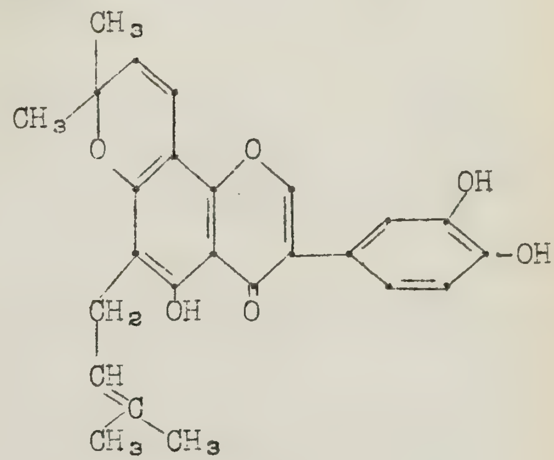
SYNTHESIS OF DIHYDRO-ISO-OSAJIN

Reported by James H. Looker February 17, 1950

Introduction: Osajin and pomiferin are two yellow pigments isolated from the fruit of the osage orange (Maclura pomifera Raf.), also called the hedge apple. The structures of osajin (I) and pomiferin (II) were established in an extensive series of investigations culminating in publication of their complete structural formulas (1). Since the pigments are so closely related, the discussion will be restricted to osajin (I).



I



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The principle evidence for the structure of osajin is found in the following considerations:

(a) Treatment of tetrahydro-osajin dimethyl ether with dilute alcoholic potassium hydroxide gives a quantitative yield of formic acid and a hydroxyphenyl-benzyl ketone. This fact demonstrates the presence of the isoflavone nucleus. Cleavage of the ketone with 30% alcoholic potassium hydroxide gives homoanisic acid and a 2,2-dimethylchroman derivative. Isolation of the acid gave proof for the 4'-hydroxyl in osajin.

(b) Osajin is isomerized by mineral acid in acetic acid to give a colorless compound containing one less hydroxyl and one less double bond than osajin. This observation demonstrates the presence of a 5-hydroxyl and an alkenyl group in position 6.

(c) Fusion of iso-osajin with 30% alcoholic potassium hydroxide gave 2,2-dimethyl-5,7-chromandiol, p-hydroxyphenylacetic acid and acetone. This observation establishes the nature of the entire carbon skeleton in osajin, except for the 2,2-dimethyl-Δ^3-chromen portion at positions 7 and 8.

(d) Neutral permanganate oxidation of an isopomiferitin derivative gave a dicarboxylic acid containing the same number of carbon atoms, thus demonstrating the presence of an endocyclic double bond. Alkaline permanganate oxidation of pomiferin gave

α-hydroxyisobutyric acid, which is characteristic of the 2,2-dimethyl-Δ^3-chromen system (2,4).

(e) Complete evidence for the position of the double bonds is found in the fact that both osajin and dihydro-osajin give acetone upon ozonolysis, and in the previously discussed demonstration of the Δ^3-chromen ring.

It should be noted th t use of pomiferin in the structure proof is permissible, since osajin and pomiferin derivatives were shown to give the same chroman derivative under strong alkaline conditions.

Synthesis of Dihydro-iso-osajin (5): The formation of dihydro-iso-osajin is depicted in the last series of equations. This substance was chosen for synthesis, since osajin itself would not be readily accessible because of the ease of isomerization to the chroman derivative.

Since dihydro-iso-osajin contains two 2,2-dimethylchroman rings, the principle methods for introducing this system into the phloroglucinol molecule were studied (A, B, C).

A. Friedel-Crafts reaction of phloroglucinol with β,β-dimethylacrylchloride, followed by Clemmensen reduction of the chromanone.

B. Allylation of phloroglucinol with γ,γ-dimethylallyl bromide in presence of zinc chloride.

C. Condensation of isoprene and phloroglucinol in glacial acetic acid with zinc chloride and sulfuric acid as catalysts.

The synthesis of the dichroman, dihydro-iso-osajinol (VII), is outlined in Chart I. To simplify the outline, the numerous isomers obtained have been omitted. The synthesis employes both methods A and B.

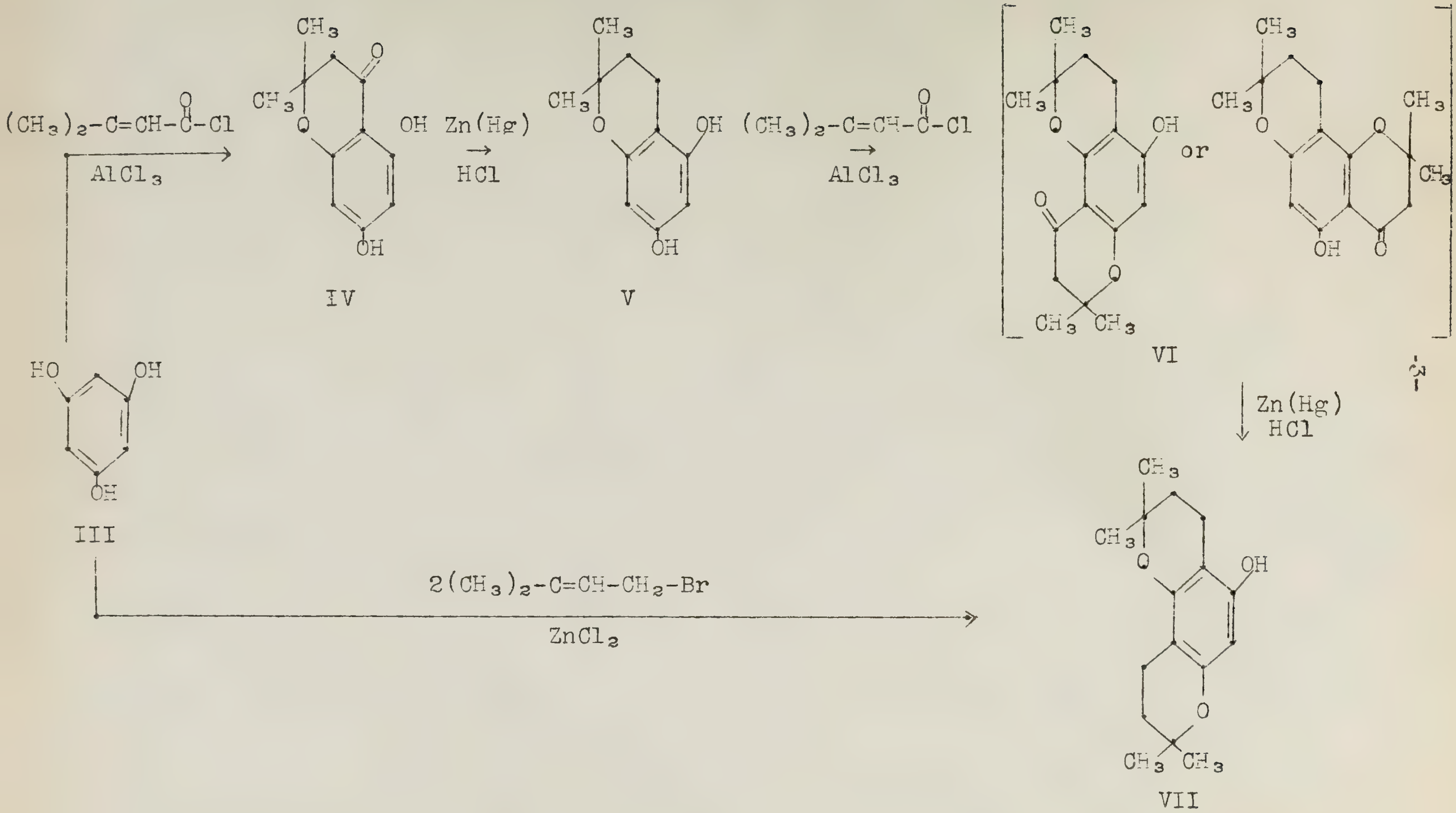
Since Compound VII had not been previously synthesized, evidence for its structure was required. This is found in conversion of VII to the trichroman (IX), as shown below. Other synthetic routes to the trichroman are also listed.

The structure proposed for VIII rests on analysis, lack of phenolic properties, formation of a mono-oxime, and method of formation. Alexander, Robertson and co-workers showed in a thorough study (2,3) that formation of the isomeric coumaranones does not occur in the type of reaction employed.

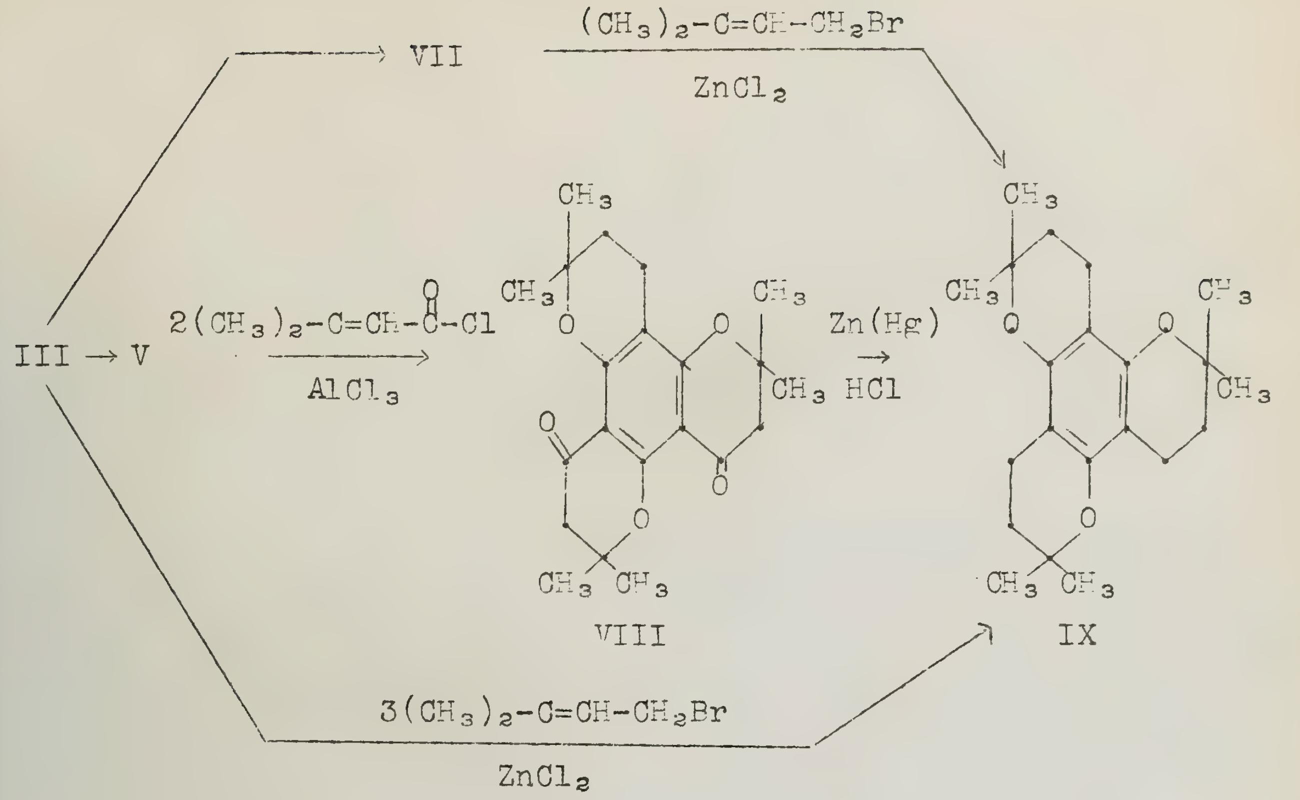
The structure proposed for IX rests upon analysis, manner of formation, and upon the following observations:

No reaction with $KMnO_4$ or Br_2 in CCl_4
Insoluble in Claisen's alkali
Negative $FeCl_3$ and hindered phenol test.

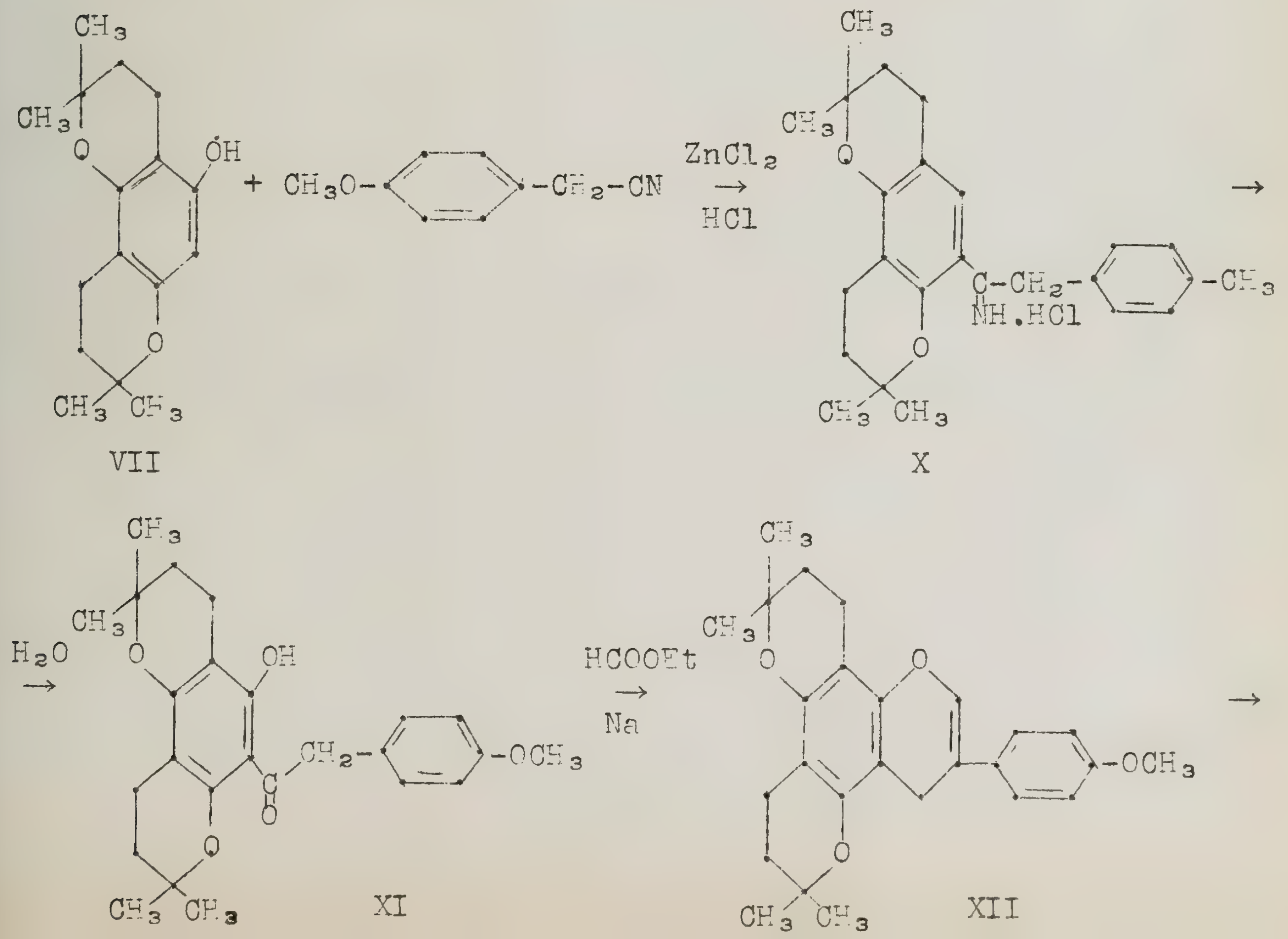
CHART I

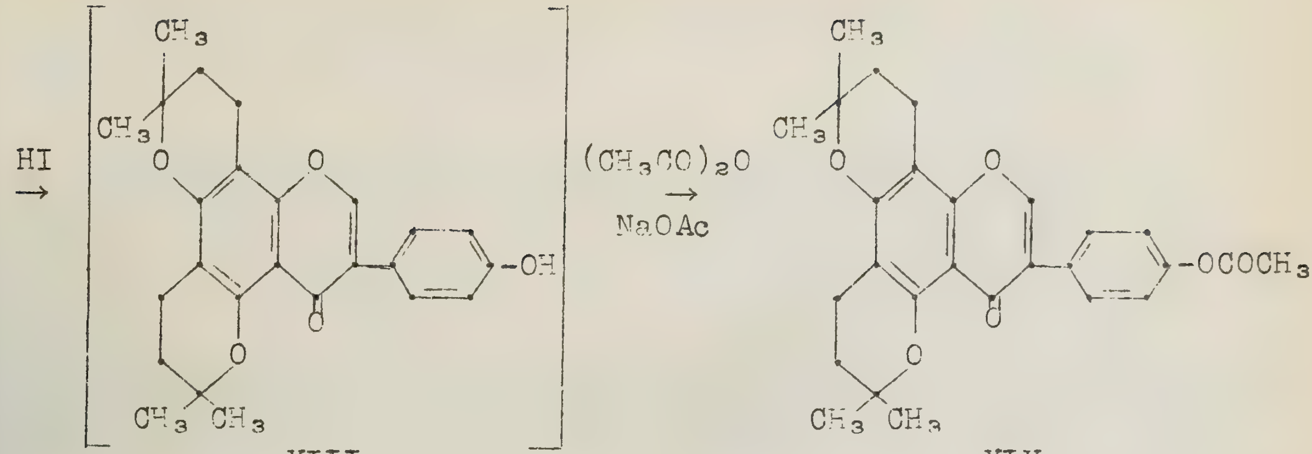


$(CH_3)_2$-C=CH-C(=O)-Cl
$AlCl_3$
IV
Zn(Hg)
HCl
V
$(CH_3)_2$-C=CH-C(=O)-Cl
$AlCl_3$
or
VI
Zn(Hg)
HCl
III
2$(CH_3)_2$-C=CH-CH_2-Br
$ZnCl_2$
VII



The remainder of the synthesis is straightforward:





XIII XIV

A Hoesch reaction between dihydro-iso-osajinol (VII) and homoanisonitrile gave the ketimine hydrochloride (X), which was hydrolyzed directly to dihydro-iso-osajetin monomethyl ether (XI). Reaction of XI with sodium and ethyl formate, the standard isoflavone synthesis, gave dihydro-iso osajin monomethyl ether (XII). Demethylation of XII gives dihydro-iso-osajin (XIII), which was characterized as the monoacetate (XIV). Derivatives XI, XII and XIV were shown to be identical with the corresponding compounds obtained from the natural product, by the usual methods of melting point and ultraviolet absorption spectra determination.

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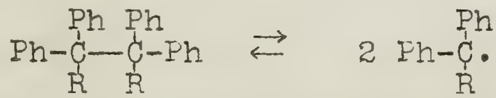
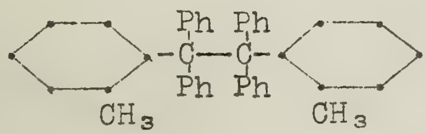
RECENT DEVELOPMENTS IN THE THEORY OF STERIC STRAIN

Reported by C. R. Walter, Jr. February 24, 1950

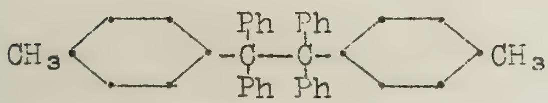
I. <u>Steric Hindrance Phenomena</u>: Dissociation of tetraphenyldialkylethanes increases with size of the alkyl groups.



Methyl groups in <u>ortho</u>-positions shown more effect on dissociation than they do in <u>meta</u>- or <u>para</u>-positions (1):



$\rightarrow$ 25% dissociation



$\rightarrow$ 5% dissociation

Carbon-carbon and boron-nitrogen bonds are isosteric and should show the same effect.

II. <u>"F-Strain"</u>: Trimethylamine is a stronger base than pyridine in a competition reaction with HCl but not with trimethylboron (2):

$$(CH_3)_3N + C_5H_5NH^+Cl^- \rightleftarrows (CH_3)_3NH^+Cl^- + C_5H_5N$$

$$(CH_3)_3N + C_5H_5N{:}B(CH_3)_3 \leftrightarrows (CH_3)_3N{:}B(CH_3)_3 + C_5H_5N$$

These reactions illustrate the "F-strain" - that strain which is caused by the steric interference of atoms or groups which are attached to different atoms resulting in a force which tends to separate them.

III. <u>"B-Strain"</u>: The Electronic theory predicts the order of increasing base strength as

$$NH_3 < CH_3NH_2 < (CH_3)_2NH < (CH_3)_3N$$

but the order actually observed is (3):

$$NH_3 < (CH_3)_3N < CH_3NH_2 < (CH_3)_2NH$$

The cause of the phenomenon is associated with the fourth nitrogen bond (4). Theoretically the three bonds of a trivalent nitrogen should be directed in space at angles of 90° to each other, but in all cases reported the angles are greater, because they must be spread to accommodate the attached groups (5,6). It

is assumed that they are spread to a value greater than the tetrahedral angle. In trivalent nitrogen derivatives such spreading of the bond angles is easy since the fourth position is vacant. However, the addition of a fourth group to the vacant position forces the nitrogen atom towards a tetrahedral configuration and results in a reduction of the expanded angles. The methyls are therefore crowded together setting up a strain in the addition compound. This effect Brown has called "B-Strain" - that strain which is introduced into the molecule brought about by the steric requirements of bulky groups attached to the central atom (3).

IV. Examples of "B" and "F"-Strain: (A) When tri-t-butylboron is used as reference acid, the sequence of base strength of the methylamines is altered to

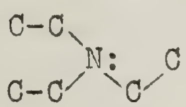
$$NH_3 < CH_3NH_2 > (CH_3)_2NH > (CH_3)_3N$$

If a reference acid of even higher steric requirements is used, the theoretically possible limit should be approached:

$$NH_3 > CH_3NH_2 > (CH_3)_2NH > (CH_3)_3N$$

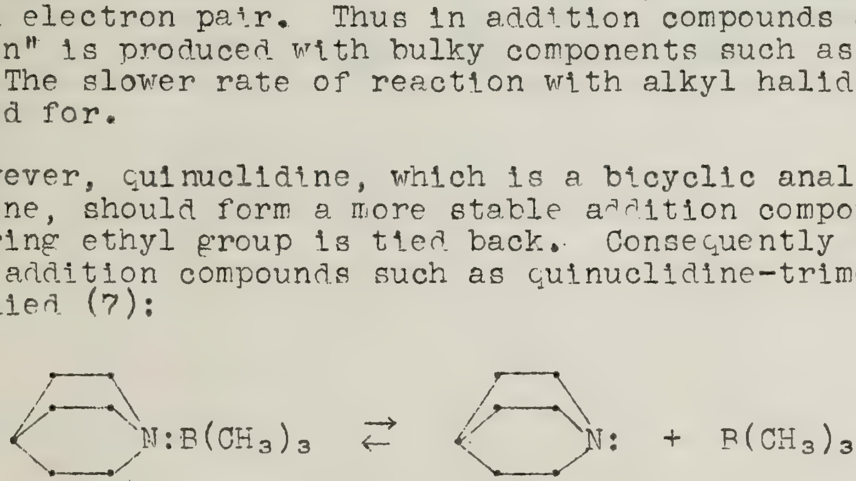
Brown and Sujishi used tri-α-naphthylboron as a reference acid, and found that the theoretical limit was indeed observed.

(B) Triethylamine is a stronger base than trimethylamine in aqueous solution (8) yet it reacts more slowly with alkyl halides (9). This is explained on the basis of the peculiar steric configuration of triethylamine (10):



One ethyl group projects into the region assigned to the unshared electron pair. Thus in addition compounds a high "F-strain" is produced with bulky components such as trimethyl boron. The slower rate of reaction with alkyl halides is similarly accounted for.

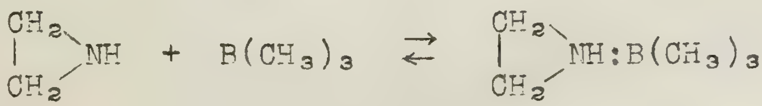
However, quinuclidine, which is a bicyclic analog of triethylamine, should form a more stable addition compound, since the interfering ethyl group is tied back. Consequently the dissociation of addition compounds such as quinuclidine-trimethylboron was studied (7):



It was found that the quinuclidine addition compound was considerably more stable than the analogous triethylamine compound.

The rate of reaction of quinuclidine with alkyl halides was faster than the same reaction with triethylamine (11).

V. "I-Strain": Brown and Gerstein (12) observed that the stability of ethylenimine-trimethylboron was less than that of the addition compounds of larger ring cyclic imines despite the fact that the F-strain in ethylenimine-trimethylboron must not be as great.



The free ethylenimine molecule may be considered to contain the strain involved in bending the two N-C bonds from their theoretical value of 90° to the 60° required by the geometry of the ring. Ethylenimine-trimethylboron may be considered to possess the greater strain involved in bending these bonds from the tetrahedral angle (109° 28') to 60°. Thus the formation of the addition compound involves an increase in ring strain.

Brown proposes that the term "I-strain" be used to describe this increase in ring strain resulting from a change in coordination number and the preferred bond angle.

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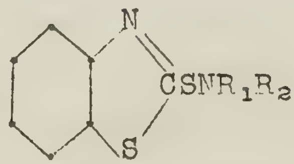
SULFENAMIDES

Reported by Ronald A Wankel February 24, 1950

I. Preparation: The discovery that benzothiazole-2-thiol is an excellent and inexpensive accelerator for the sulfur vulcanization of rubber has stimulated the study of many types of 1-thiazole-2-thiol derivatives (1,2). Among these, some benzothiazolesulfenamides (I) have been shown to be of outstanding value as delayed-action, self-activating accelerators in both natural and synthetic rubbers (3).

(I) 

One of these compounds was developed in Germany shortly before the last war as "Vulkacit AZ" (R_1=R_2=ethyl). A parallel but independent development in this country resulted in large scale production and use of "Santocure" (R_1=hydrogen, R_2=cyclohexyl).

A recent review covers rather completely the synthesis of sulfenic acids and their derivatives except for some recent and important work (4,5). Synthesis of sulfenamides from the sulfenic acids is impractical because, with very few exceptions, these acids are either unknown or very unstable. However, many sulfenyl halides are quite stable and react with amines to form sulfenamides (6).

A) $RSX + R_1R_2NH \rightarrow RSNR_1R_2 + HX$

The aromatic sulfenyl chlorides, especially the nitrophenyl derivatives, are the most stable and many sulfenamides have been prepared from these chlorides. Similarly, thiazolesulfenyl halides should react with amines to form the corresponding sulfenamide. This reaction was reported for benzothiazolesulfenyl chloride, but the product with a primary amine was the bis-benzothiazole sulfenimide, rather than the expected mono-substituted amide (7).

B) $2RSX + R_1NH_2 \rightarrow (RS)_2NR_1 + 2HX$

Certain thiazole sulfenamides have been prepared by the reaction of metallic thiazolyl mercaptides with N-chloro derivatives of secondary amines (8).

C) $RSM + R_1R_2NX \rightarrow RSNR_1R_2 + MX$

This method is not very convenient because of the difficulties involved in the preparation and handling of N-monochloro derivatives of the more common amines.

Another preparation is the reduction of the corresponding thiazolyl disulfide with ammonia or amines (9).

D) $$RSSR + 2R_1R_2NH \rightarrow RSNR_1R_2 + RSH \cdot R_1R_2NH$$

The obvious disadvantage in this process is that only half of the thiazolyl disulfide molecule is utilized and the sulfenamide must be separated from the ammonium thiazolyl mercaptide.

A new process consists of the direct oxidative condensation of an amine and a metallic thiazolyl mercaptide in aqueous solution (10,11,12). The best oxidizing agents are the halogens or sodium hypochlorite.

E) $$R_1SNa + RNH_2 + X_2 + NaOH \rightarrow R_1SNHR + 2NaX + H_2O$$

F) $$R_1SNa + RNH_2 + NaOCl \rightarrow R_1SNHR + NaCl + NaOH$$

The usual process utilizes an excess of the amine in an aqueous solution containing the sodium salt of the mercaptothiazole with some additional alkali. The temperature is kept between 5 and 30°C, while the oxidizing agent is slowly added. The optimum pH is 12.0 to 12.5. If the solution is too strongly basic, a pure product is formed but in smaller yields, while at a pH of less than 12, 2-benzothiazolyl disulfide is invariably found as an impurity.

G) $$2R_1SNa + X_2 \rightarrow R_1SSR_1 + 2NaX$$

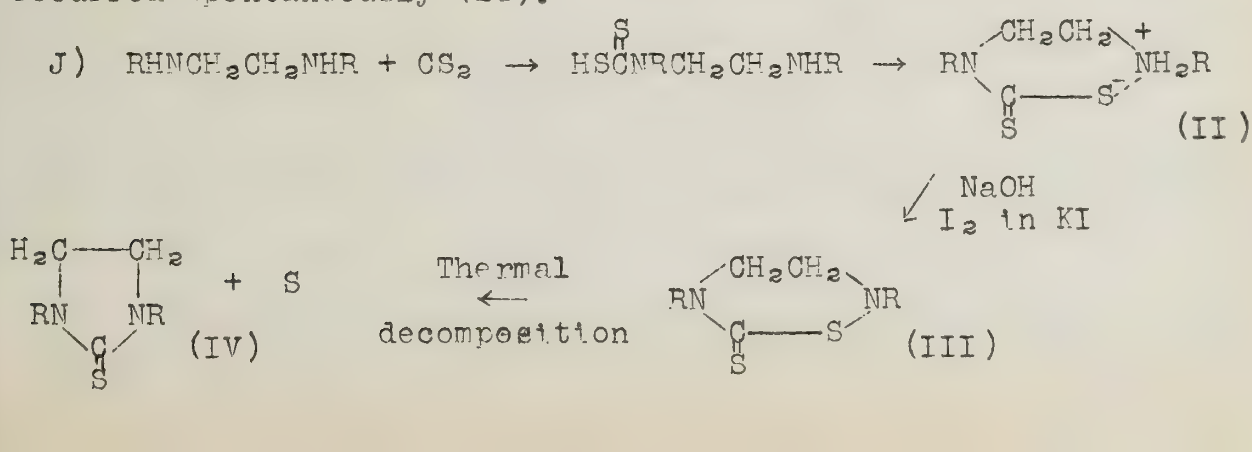
In general, the yields range from 70 to 95%, utilizing a 3 to 5 mole excess of the amine.

Dialkyl mono amines react with carbon disulfide to form salts of dialkyldithiocarbamic acids, which may be oxidized in the presence of another amine to give substituted dialkylthiocarbamyl sulfenamides (13,14).

H) $$RR_1NH + CS_2 \xrightarrow{NaOH} RR_1N\overset{S}{\overset{\|}{C}}SNa \xrightarrow[(O)]{R_2R_3NH} RR_1N\overset{S}{\overset{\|}{C}}-S-NR_2R_3$$

When N,N' dialkylethylenediamines are treated with carbon disulfide in benzene or acetone, the highly exothermic formation of the N-alkyl-N-(β-alkylaminoethyl)dithiocarbamic acid inner salts occurred spontaneously (14).

J)



These salts (II) are insoluble in the usual organic solvents, but could be purified by solution in weak ammonia followed by volatization of the ammonia at room temperature. Oxidation with iodine (in KI) in the presence of sodium hydroxide gave a new type of compound, the tetrahydro-1,2,3,5 thiadiazine-6-thiones (III). These new heterocyclic compounds may be considered as cyclic thiocarbamylsulfenamides. When heated gently, these compounds decompose to 1,3 dialkyl-2-imidazolidinethiones (IV).

II. Properties: The sulfenamides are, in general, rathern unstable compounds, decomposing on standing for several days, even when dry. The decomposition products are usually disulfides and substituted ammonium mercaptides. The thiocarbamylsulfenamides, however, decompose to give thioureas and sulfur.

K) $R_1R_2N\overset{\overset{S}{\|}}{C}SNR_3R_4 \rightarrow R_1R_2N\overset{\overset{S}{\|}}{C}NR_3R_4 + S$

N,N-Dimethylthiocarbamyl-N'-cyclohexylsulfenamide (R_1=R_2=methyl, R_3=hydrogen, R_4=cyclohexyl) decomposes on heating to give N,N'-dicyclohexylthiourea. An amine exchange reaction evidently takes place with volatilization of dimethylamine and replacement by cyclohexylamine. Light and heat accelerate the rate of decomposition. The presence of free alkali also catalyzes this decomposition, thus making it necessary to free the products entirely from the alkali of the reaction mixture. The thiazolesulfenamides are somewhat resistant to strong alkali, however, but not to acidic substances which decompose these sulfenamides in aqueous solution or dry ether with the formation of disulfides and the amine salt of the acid used.

Stability depends on the nature of the amine, secondary amines forming more stable amides than primary amines. Cyclohexylamine and several heterocyclic amines, such as piperidine, form the most stable amides. Benzothiazole-2-thiol forms a more stable amide than the alkyl and unsubstituted thiazole-2-thiols (12).

III. Reactions: Sulfenamides are found in many cases to react with acetic anhydride to give the acetylated derivative (V), while a similar reaction with acetyl chloride usually gives only the disulfide (12).

L) $RSNHR + (CH_3CO)_2O \rightarrow RSNRCOCH_3$ (V)

M) $RSNHR + CH_3COCl \rightarrow RSSR$

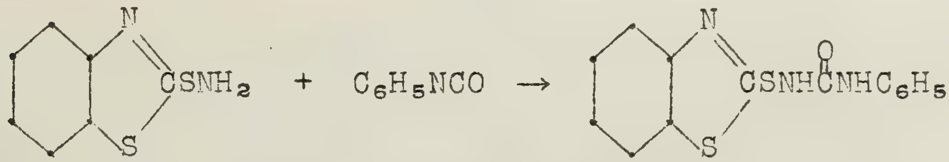
Many unsubstituted sulfenamides react with amines to form substituted sulfenamides, in an amine exchange type of reaction (12).

N) $RSNH_2 + R_1R_2NH \rightarrow RSNR_1R_2 + NH_3$

This type of reaction is very convenient, in many cases, for the preparation of certain sulfenamides otherwise difficult to prepare (11,12).

Benzothiazole-2-sulfenamide reacts with phenylisocyanate to form N-phenylcarbamylbenzothiazole-2-sulfenamide

O)



However, N-cyclohexylbenzothiazole-2-sulfenamide gave N-phenyl-N'-cyclohexyl urea under similar treatment with phenylisocyanate.

Carbon disulfide reacts with the sulfenamides to form the thiol and the corresponding isothiocyanate (12).

P) $RSNHR_1 + CS_2 \rightarrow RSH + R_1NCS + S$

This reaction offers a unique and convenient new method for the preparation of substituted isothiocyanates.

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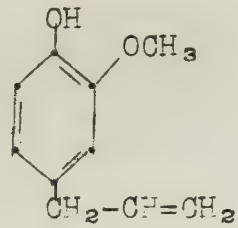
CONSTITUENTS OF THE OIL OF WILD CLOVES

Reported by Bernard H. Braun   March 3, 1950

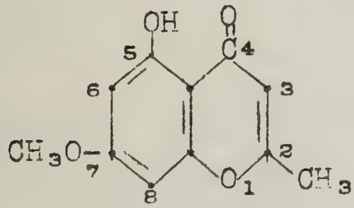
Stimulated by the fact that wild cloves possess a different odor than cultivated ones, a study of the constituents of the essential oil of the wild tree was made (1). It was noted at once that eugenol (I) $C_{10}H_{12}O_2$, the chief constituent (60-85%) of the oil of the cultivated tree, was absent in that of the wild one.



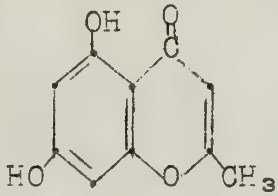
I

Instead, two new compounds eugenin (II) $C_{11}H_{10}O_4$ and eugenone (III) $C_{10}H_{12}O_4$, later (2) corrected to $C_{13}H_{16}O_5$ were isolated, and in later work in addition eugenitin (IV) $C_{12}H_{12}O_4$ (4) and isoeugenitol (V) $C_{11}H_{10}O_4$ (5) were isolated. The original work (1) led to incorrect formulae for both (II) and (III), but the discrepencies were noted and corrected in research leading to the synthesis of eugenone (2) and eugenin (3).

Eugenin (II) $C_{11}H_{10}O_4$ = $C_9H_3O_2(-CH_3)(-OCH_3)(-OH)$ shows the reactions of a hindered phenol (ferric chloride solution → violet color; the compound dissolves slowly in hot alkali; diezomethane is without effect; a monoacetate no longer reacting with $FeCl_3$ can be made); treatment with hydriodic acid leads to the known (VI).



II



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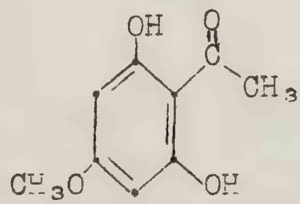
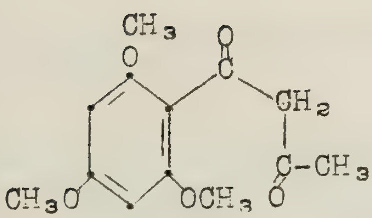


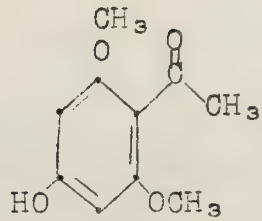
VII

(this was at first confused with the isomeric coumarin which has very similar properties (1) and a false structure was assigned to (II) on this basis). The fact that CH_2N_2 is without effect shows the free hydroxyl must be at 5, where it is deactivated by hydrogen bond formation. This conclusion was confirmed by observing that alkali fusion led to the known (VII). The proposed structure (II) was confirmed by synthesis by treating synthetic (VI) (7) with diezomethane (2).

Eugenone (III) $C_{13}H_{16}O_5$ = $C_8H_7(OCH_3)_3(CO)_2$ (at first regarded as $C_{10}H_{12}O_4$ (1), but different from synthetic VIII (6)) is an enol (ferric chloride → dark red; soluble in alkali) (at the first study this was mistaken for a phenolic hydroxyl) giving the



III

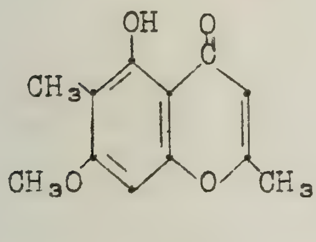


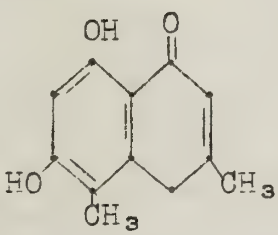
VIII

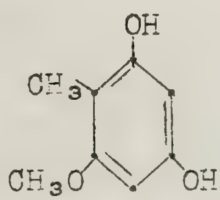
characteristic reactions of 1:3 diketones ($\underline{p}$-nitrophenylhydrazine, and Girard's reagent "P" $NH_2NHCONC_5H_5Cl^-$ react to give pyrazoles; Cu^{++} forms a green salt); HI → (VI) (by demethylation and internal dehydration of the enol form); the iodoform reaction is positive. The structure (III) following from this was confirmed by synthesis, following (7).

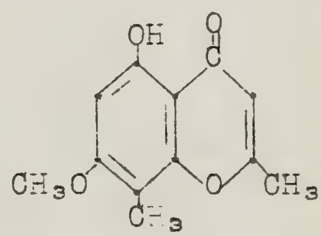
$$(CH_3O)_3C_6H_2COCH_3 + CH_3COOC_2H_5 \xrightarrow{Na} (III) \quad (3)$$

Eugenitin (IV) $C_{12}H_{12}O_4 = C_{11}H_8O_2(OH)(OCH_3)$ shows the same reactions as (II), of which it is the next homolog. Boiling with dilute alkali → acetone and the known (IX) which shows the pattern of methylation. HI → $C_{11}H_{10}OH$ (V) which is not the desmethyl com-



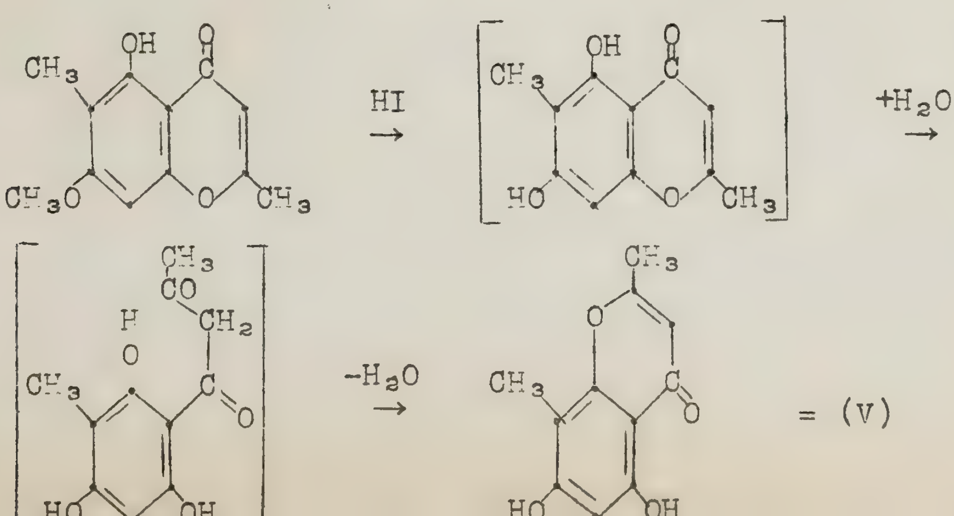






IV V IX X

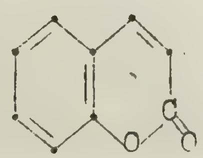
pound, since its dimethyl ether differs from eugenitin methyl ether. (The hindered 5 position is methylated with $(CH_3)_2SO_4$ and alkali). The isoeugenitin (X) is more soluble in alkali than the more hindered eugenitin (IV), confirming the assignment of structure. The transformation by HI is due to ring opening and subsequent closure at the other hydroxyl. This ring closure of ortho

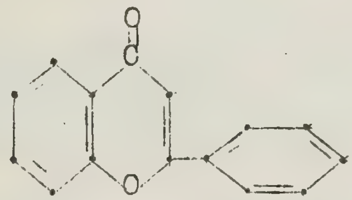


hydroxy-benzoyl-acetones with HI is a well-known synthesis of 2-methyl-chromones (4).

Isoeugenitol (V) $C_{11}H_{10}O_4$ was subsequently discovered in the natural oil (5). Its synthesis has been accomplished, but not yet described, according to a note in the article promising details in a forthcoming publication.

These four compounds are rather unusual. Eugenone is the first natural benzoyl-acetone derivative found, while the other three compounds belong to the rare class of chromones. (The isomeric coumarins and the flavones, on the other hand, are very common.)





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TETRAFLUOROETHYLENE

Reported by William D. Emmons March 3, 1950

Preparation: One of the most important developments in the field of fluorine chemistry in the past few years has been the discovery of the wide variety of reactions which tetrafluoroethylene will undergo. This substance was first characterized by Ruff and Bretschneider (1) who prepared it from tetrafluoromethane. It has also been prepared by dechlorination of sym-dichlorotetrafluoroethane (2). The best synthesis that has been reported to date, however, is the high temperature, non-catalytic pyrolysis of monochlorodifluoromethane (3).

$$2CF_2HCl \rightarrow CF_2{=}CF_2 + 2HCl$$

The reaction is run in an inert tube around 650°C., and under optimum conditions the yield approaches 90-95%. Tetrafluoroethylene has an unusually reactive double bond and has been shown to participate in vinyl polymerization, cycloalkylation, and in many addition reactions.

Vinyl Polymerization: The polymerization of tetrafluoroethylene is carried out under superatmospheric pressure in the presence of water and such polymerization initiators as persulfates, hydrogen peroxide, oxygen, or organic peracids (4). The product is a highly crystalline linear polymer which is characterized by

$$CF_2{=}CF_2 \xrightarrow[H_2O_2-H_2O]{700\ lbs/in^2} -(CF_2CF_2)_x-$$

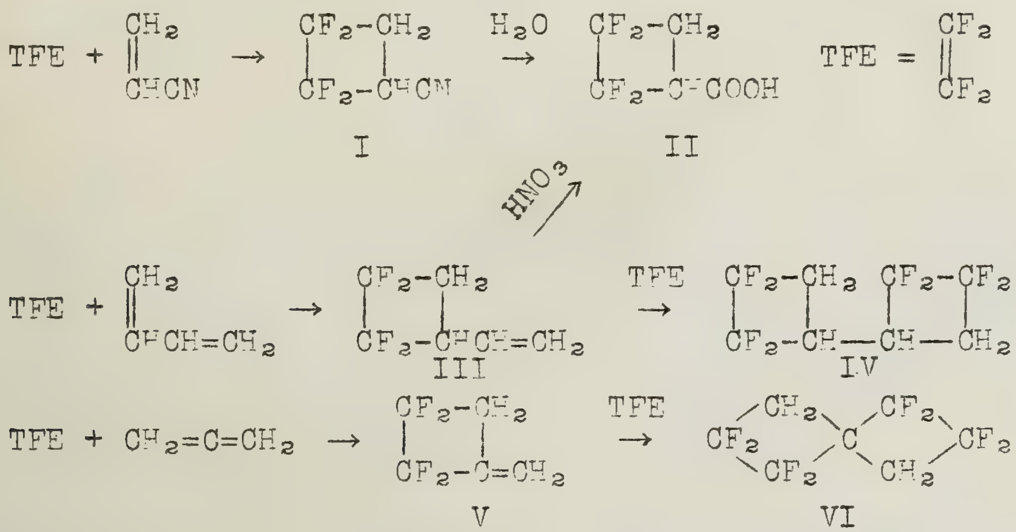
extreme toughness over a wide range of temperature, chemical inertness, and heat resistance. It has no true melting point but undergoes a solid transformation at 620°F. with a sharp drop in strength. It is transparent in thin sections and is marketed under the trade name of Teflon.

Cycloalkylation: Perhaps the most interesting reaction of tetrafluoroethylene is cycloalkylation (5). Thus it has been shown that the fluoroolefin reacts with a wide variety of olefins to form tetrafluorocyclobutanes. With ethylene itself tetrafluorocyclobutane is produced in 40% yield. The reaction takes place

$$CF_2{=}CF_2 + CH_2{=}CH_2 \rightarrow \begin{array}{l} CF_2-CH_2 \\ | \quad\quad\ \ | \\ CF_2-CH_2 \end{array}$$

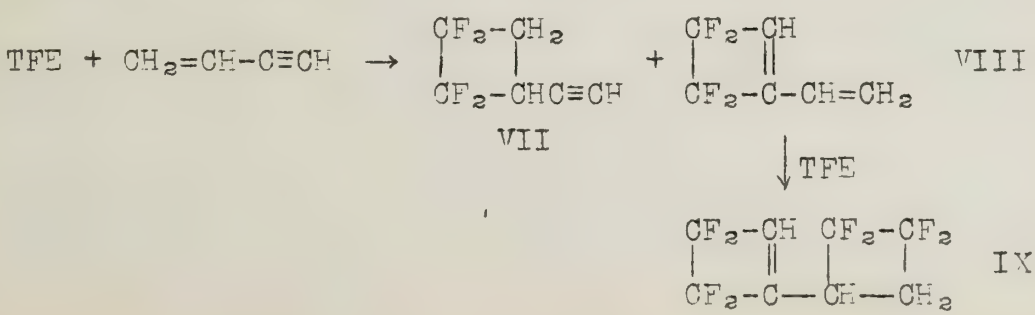
under the influence of a small amount of polymerization inhibitor such as hydroquinone together with heat and pressure. Generally a temperature of 150°C. and a pressure of around 50 atmospheres are employed. The cycloalkylation reaction occurs at a lower temperature and apparently with greater facility than does

polymerization. A wide variety of olefins have been employed in the reaction. Thus acrylonitrile gives in 84% yield I which can be hydrolyzed to the corresponding acid. Butadiene reacts to



give either III or IV depending on the temperature. Allene also reacts with either one or two moles of TFE forming V and VI, the latter being a fluorospirane. III and V can of course be hydrogenated, and use of this was made in assignment of structure. The structure proofs of these compounds are based on their mode of formation, composition, and properties, as well as the inter-relations of certain of the compounds. Thus the infrared spectrum shows no carbon carbon double bond in tetrafluorocyclobutane. The cyclobutane ring in these products is amazingly stable. Furthermore it is interesting to note that while an aliphatic side chain fluorine atom can generally be hydrolyzed off, the fluorine atoms in tetrafluorocyclobutane are extremely resistant to hydrolysis.

Cycloalkylations with tetrafluoroethylene and enynes proceed with participation of both the ethylenic and the acetylenic group of the enyne. Thus with monovinylacetylene the reaction proceeds as indicated. VII and VIII were the chief products formed and were obtained in approximately equal amounts.



<u>Addition reactions</u>: Tetrafluoroethylene takes part in a wide variety of addition reactions, particularly with compounds having an active hydrogen (6). In the presence of a small amount of sodium alkoxide the olefin reacts with alcohols to form the corresponding alkyl ether. With ethyl alcohol the yield is 93%.

$$CF_2{=}CF_2 + ROH \xrightarrow{RONa} HCF_2CF_2OR$$

In some reactions of this type, derivatives of difluoroacetic acid are obtained rather than the tetrafluoroethane compound. The mechanism of this reaction was indicated when it was found that reaction with sodium bisulfite gave both types of products, sodium tetrafluoroethanesulfonate and sodium difluoroacetate. The difluoroacetate apparently results from the susceptibility of the α-fluorine atoms to hydrolysis. With amines a similar type of

$$CF_2{=}CF_2 + NaHSO_3 \rightarrow HCF_2CF_2SO_3Na$$

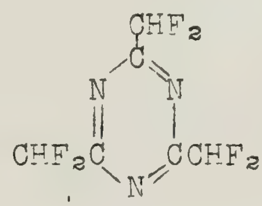
$$HCF_2CF_2SO_3Na \xrightarrow{H_2O} [HCF_2COSO_3Na + 2HF] \rightarrow HCF_2COONa + SO_2$$

reaction apparently occurs via the intermediate tetrafluoroamine

$$CF_2{=}CF_2 + RNH_2 \rightarrow [HCF_2CF_2NHR] \rightarrow HCF_2CONHR$$

which is hydrolyzed to a difluoroacetamide. With ammonia the reaction is similar but involves the formation of difluoroacetonitrile which then trimerizes forming a triazine.

$$CF_2{=}CF_2 + NH_3 \rightarrow [HCF_2CN] \rightarrow$$



With formaldehyde tetrafluoroethylene forms α,α difluorohydracrylic

$$CF_2{=}CF_2 + CH_2O + H_2O \rightarrow [HOCH_2CF_2CF_2OH] \rightarrow HOCH_2CF_2COOH$$

acid. It is interesting to note that while iodine will not add to tetrachloroethylene it will do so with the fluorine analog, forming sym-diiodotetrafluoroethane.

Recently it has also been shown that halomethanes will add to tetrafluoroethylene in the presence of aluminum chloride to form chlorofluoropropanes (7). Typical examples are the additions of chloroform and carbon tetrachloride in which the yields are respectively 83% and 88%.

$$CHCl_3 + CF_2{=}CF_2 \rightarrow CHCl_2CF_2CF_2Cl$$

$$CCl_4 + CF_2{=}CF_2 \rightarrow CCl_3CF_2CF_2Cl$$

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RECENT MODIFICATIONS OF THE STOBBE CONDENSATION

Reported by Frank B. Hauserman March 3, 1950

Introduction: The Stobbe Condensation involves the reaction of a carbonyl compound, generally a ketone, an ester of the succinic acid type, and the proper catalyst, with the formation of the half ester of an unsaturated acid.

$$\begin{array}{l} R \\ \quad \rangle C{=}O \\ R \end{array} + \begin{array}{l} CH_2\text{-}COOR' \\ | \\ CH_2\text{-}COOR' \end{array} \xrightarrow{\text{catalyst}} \begin{array}{l} R \\ \quad \rangle C{=}C\text{-}CH_2COOH \\ R \qquad\; COOR' \end{array}$$

Since the previous reports on this condensation (1,2), several papers have been published (3,4,5,6,8,10), which give further modifications of the reaction as well as additional information as to its mechanism.

Catalyst and Succinic Ester Modifications: The previous report (2) discusses the use of potassium t-butoxide as the catalyst in place of sodium ethoxide with a resulting improvement in the condensation. Recently it was shown (3) that sodium hydride has certain advantages over potassium t-butoxide as catalyst, as it is considerably easier to use and the yields are at least as good.

If di-t-butyl succinate is used instead of the diethyl ester (4), the yields are often a little better, and more important, the use of a large excess of the ester is unnecessary as the rate of self-condensation of the t-butyl ester is considerably lower than that of the ethyl or methyl ester. Thus, in the condensation of p,p'-dimethoxybenzophenone with di-ethyl succinate only a 43% yield of the half ester is obtained unless an additional charge of the ester and catalyst, equivalent to the starting amounts, is added. With di-t-butyl succinate only a single charge is necessary to obtain an 89% yield. However, if the ketone used is strongly enolizable, the yield of the half ester is very poor, regardless of the reactants. Thus desoxybenzoin gives only a 19% yield at the best.

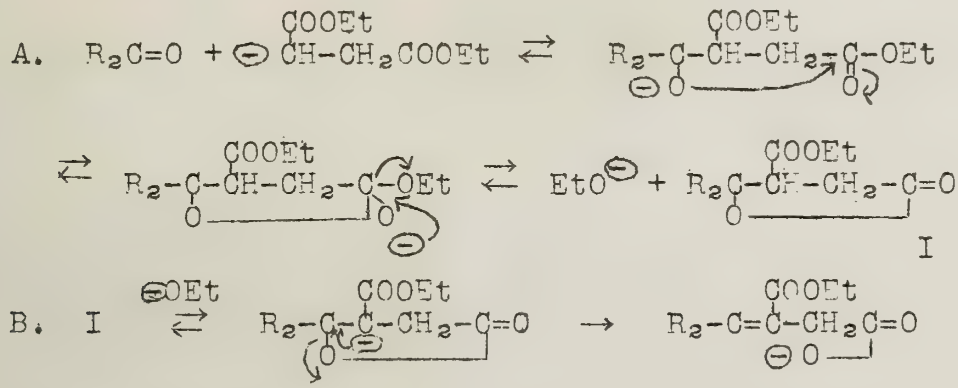
The di-t-butyl succinate is prepared by a new method, which involves ester interchange of diphenyl succinate (prepared from succinic acid, phenol, and phosphorus oxychloride in benzene) with potassium or sodium t-butoxide. The overall yield (65%) is more than double that obtained in other preparations.

Mechanism (8): It is of importance to note that this condensation is limited almost entirely to succinic acid type esters. Thus, with benzophenone, ethyl or t-butyl acetate do not react at all and diethyl malonate does not condense to any appreciable extent under the conditions of the reaction. This specificity of succinic esters may be due to the fact that the carbethoxyl group is readily available for easy ring formation.

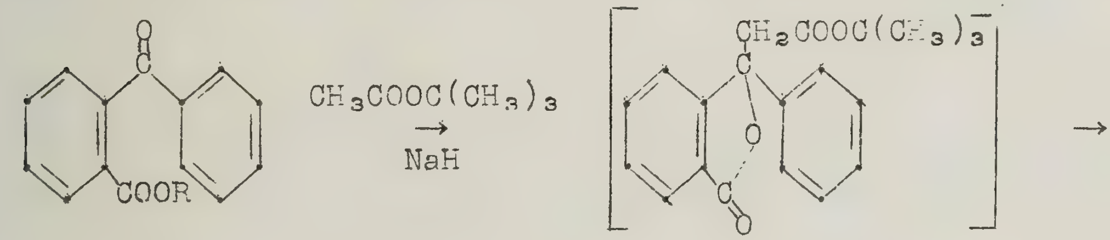
Stobbe postulated an intermediary paraconic ester (I) in order to explain this reaction (9). Since then much evidence has

been accumulated supporting this postulate.

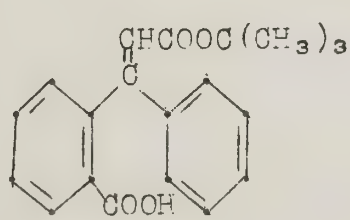
Paraconic esters have been isolated from Stobbe Condensations and they are readily cleaved by alkoxides, in excellent yields, to salts of the unsaturated half esters. This cleavage, a β elimination, is shown in B below, and the irreversible step drives the reaction to completion. A and B together give the course of the condensation.



The condensation of o-benzoyl benzoate (II) with t-butyl acetate in the presence of sodium hydride gives the half ester IV (8). Since this condensation fails with benzophenone, the participation of an intermediary lactone ester (III) is postulated. This gives further support for the above mechanism.



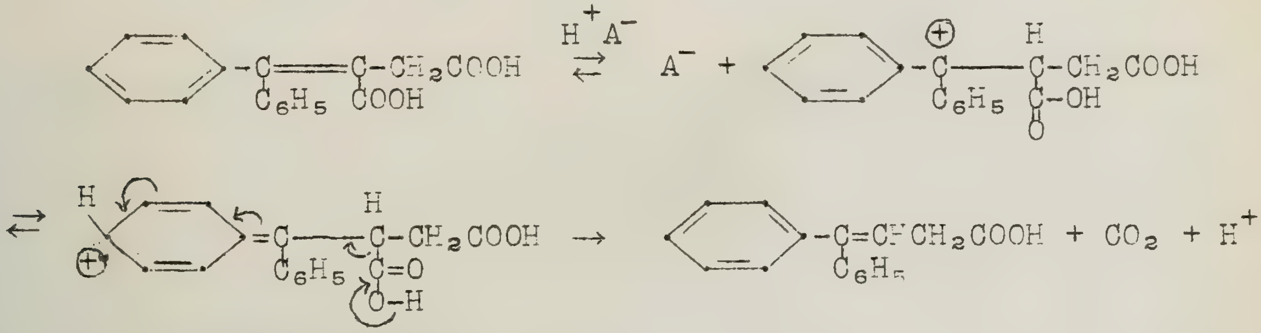
II III



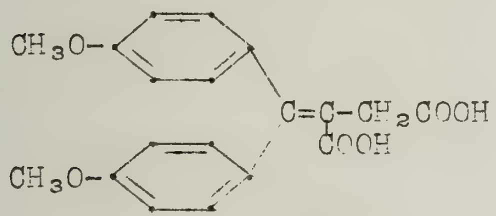
IV

Esters of glutaric acid do not undergo the Stobbe Condensation to any appreciable extent. Thus, di-t-butyl glutarate gives only a 10% yield of the half ester when condensed with benzophenone in the presence of sodium hydride. This may be due to the fact that the δ lactone ring may not be formed as readily as the γ lactone ring, thus allowing competing reactions such as self-condensation to take place preferentially.

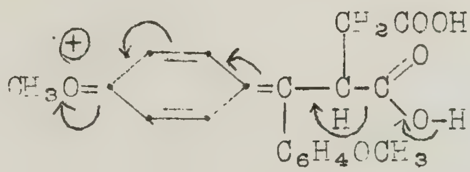
Decarboxylation and Lacto-Enoic Tautomerism: A mechanism for the acid catalyzed decarboxylation of the unsaturated dibasic acids of the cinnamic acid type has been advanced (5), involving a β carbonium ion:



If this mechanism, involving a β carbonium ion is correct, then γ,γ-di-p-anisylitaconic acid (VI) would be expected to undergo decarboxylation more readily than the γ,γ-diphenylitaconic acid (V), as the methoxy group should facilitate this reaction through some intermediate such as VII.



VI

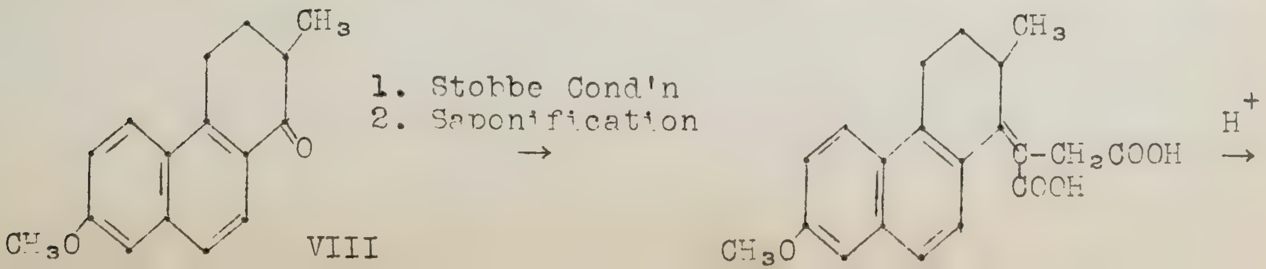


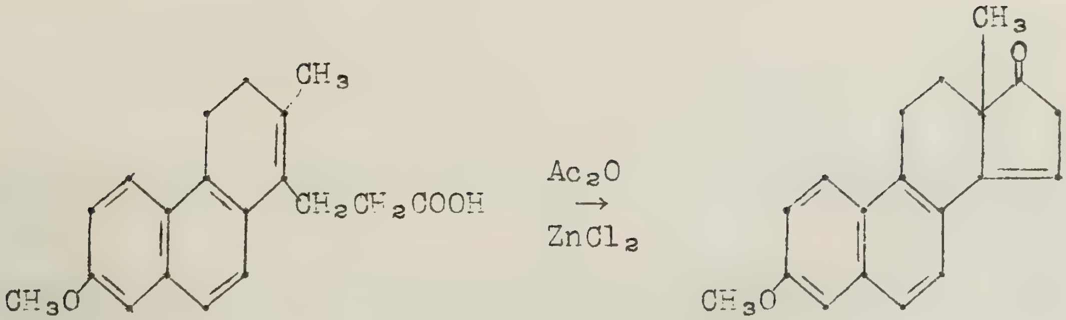
VII

It was found (6) that the methoxy groups have a striking effect on decarboxylation, for with a 3:2:1 mixture of acetic acid, 48% hydrobromic acid and water, decarboxylation of VI was 90% complete in two minutes as compared with two hours for the parent compound V.

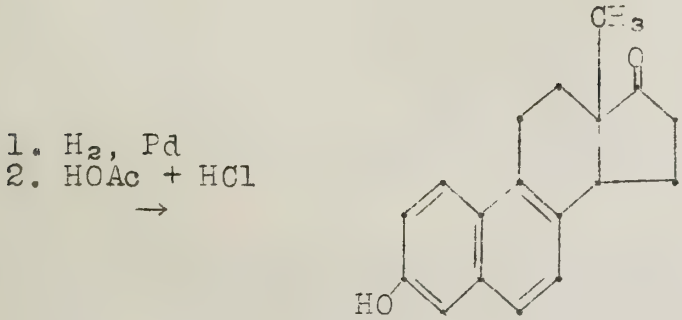
As reported earlier (2,7), the unsaturated acid obtained on decarboxylation is in equilibrium with the saturated γ lactone, and both compounds are readily interconvertible.

A New Synthesis of Equilenin (10): By use of this condensation 14,15-dehydroequilenin methyl ether (IX) can be prepared from 1-keto-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene (VIII), and IX in turn can be converted to equilenin (X), a naturally occurring steroid (11). The steps in the synthesis are as follows:





IX



X

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UNSATURATED SULFONES

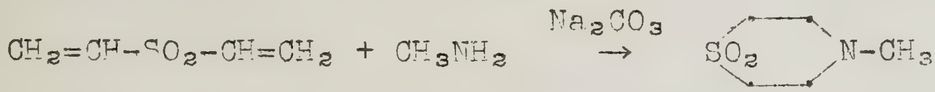
Reported by Charles N. Winnick March 3, 1950

Investigation of the linear unsaturated sulfones has been carried out largely in connection with studies on mustard gas (β,β'-dichlorodiethyl sulfide).

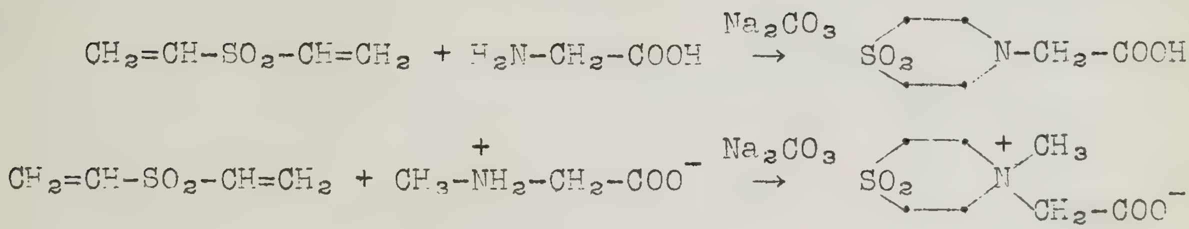
Divinyl sulfone is a highly reactive compound which can be prepared from β,β'-dichlorodiethyl sulfone by the action of triethylamine (1), water (2), or zinc powder (3). The β,β'-dichlorodiethyl sulfone is easily obtained from the corresponding sulfide by oxidation with hydrogen peroxide. It is interesting to note that divinyl sulfide cannot be oxidized to the sulfone with hydrogen peroxide (4) although perbenzoic acid brings about the oxidation (5). Vinyl-aryl and vinyl-alkyl sulfides, however, can be oxidized with hydrogen peroxide to the sulfone (6). Divinyl sulfone and β,β'-dichlorodiethyl sulfone give identical products in many reactions.

The α,β unsaturated sulfones add halogens and halogen acids very slowly, if at all. Divinyl sulfone does not react with hydrogen chloride under any conditions, but will add hydrogen bromide slowly to yield the expected β,β'-dibromodiethyl sulfone (1). Bromine adds very slowly to divinyl sulfone, 2-chloroethyl vinyl sulfone, and p-tolyl vinyl sulfone (2). The addition of bromine to ethyl vinyl sulfone is catalyzed by ultra-violet light (7). The resulting compounds lose hydrogen bromide readily.

Divinyl sulfone tends to form cyclic compounds with primary amines and amino acids (2). The addition of many primary and secondary amines to aryl-vinyl sulfones has been effected (8).

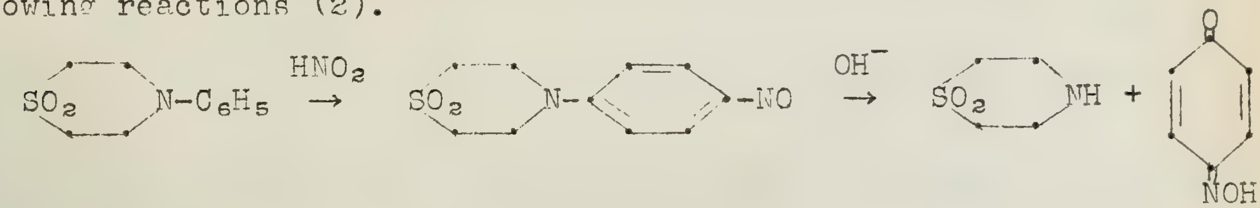


4-methyl tetrahydrothiazine 1,1-dioxide

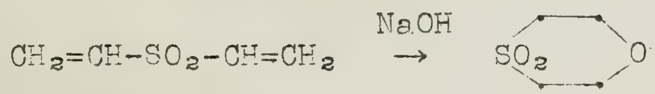


The reaction with sarcosine to yield a betaine indicates that the tendency to cyclize is indeed strong. Similar betaines are formed from proline, piperidine-2-carboxylic acid, and N-methyl sulfanilic acid. Cysteine reacts through its thiol group giving a linear product. Aniline forms both the cyclic and linear compounds (1).

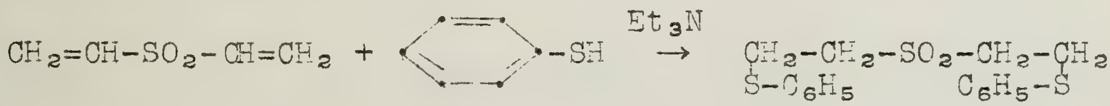
The parent compound of this series cannot be made from divinyl sulfone and ammonia, but has been synthesized by the following reactions (2).

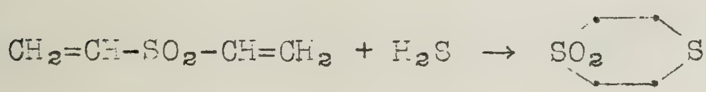


Divinyl sulfone forms tetrahydrothioxin-4,4-dioxide when treated with aqueous sodium hydroxide. Some linear dihydroxy compound is formed with aqueous sodium carbonate (2).



Thiols react vigorously with divinyl sulfone providing a trace of a basic substance is present. Hydrogen sulfide yields a small amount of the dithiane-1,1-dioxide together with large amounts of polymers (1). The addition of hydrogen sulfide and mercaptans to unsaturated sulfones is the subject of a German patent (9). Sodium methoxide in methyl alcohol forms a linear dimethoxy compound.





$$CH_2{=}CH{-}SO_2{-}CH{=}CH_2 + NaOCH_3 \xrightarrow{CH_3OH} CH_3O{-}CH_2{-}CH_2{-}SO_2{-}CH_2{-}CH_2{-}OCH_3$$

Phenyl vinyl sulfone has been prepared in the following manner, which is a standard method for mono-vinyl sulfones (10).

$$C_6H_5SH + Cl{-}CH_2{-}CH_2{-}OH \rightarrow C_6H_5{-}S{-}CH_2{-}CH_2{-}OH \xrightarrow{SOCl_2} C_6H_5{-}S{-}CH_2{-}CH_3{-}Cl$$

$$\xrightarrow{H_2O_2} C_6H_5{-}SO_2{-}CH_2{-}CH_2{-}Cl \xrightarrow{Et_3N} C_6H_5{-}SO_2{-}CH{=}CH_2$$

The addition of sodium bisulfite to compounds of the type $R{-}SO_2{-}CH{=}CH_2$ where R is an alkyl group larger than six carbons, gives sulfonates (11). The addition of nitro-paraffins to unsaturated sulfones has been investigated (12). n-Butyl vinyl sulfone is used as an example. Divinyl sulfone and nitroethane do not give the cyclic compound but only polymers.

$$CH_2{=}CH{-}SO_2{-}R + NaHSO_3 \longrightarrow R{-}SO_2{-}CH_2{-}CH_2SO_3Na$$

$$\underline{n}{-}Bu{-}SO_2{-}CH{=}CH_2 + CH_3CH_2NO_2 \xrightarrow{\text{Cat. KOH}} O_2N{-}\underset{CH_3}{\underset{|}{C}}{-}(CH_2{-}CH_2{-}SO_2{-}\underline{n}Bu)_2$$

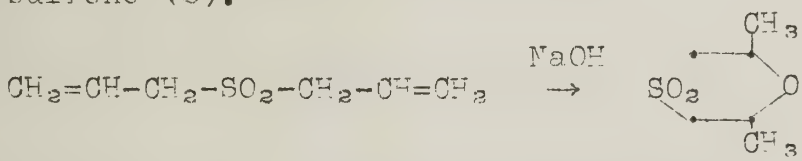
$$\underline{n}{-}Bu{-}SO_2{-}CH{=}CH_2 + CH_3CH_2NO_2 \xrightarrow{\text{1 Equiv KOH}} O_2N{-}\underset{CH_3}{\underset{|}{CH}}{-}CH_2{-}CH_2{-}SO_2{-}\underline{n}Bu$$

The reaction of sulfinates with unsaturated alkyl halides is another route to unsaturated sulfones particularly suited to allyl sulfones (3),

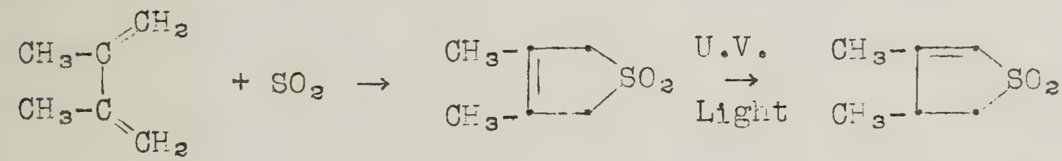
$$C_6H_5{-}CH_2{-}SO_2Na + CH_2{=}CH{-}CH_2Br \longrightarrow C_6H_5{-}CH_2{-}SO_2{-}CH_2{-}CH{=}CH_2$$

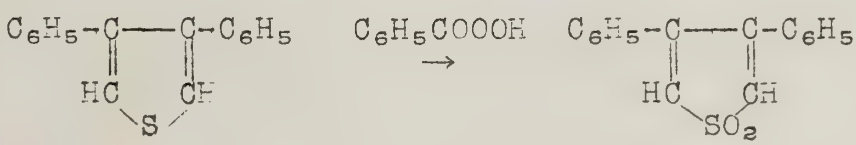
The reactions of divinyl sulfide and divinyl sulfoxide have also been investigated. In general, the sulfide does not give cyclic compounds as readily as the sulfone. The sulfoxide is intermediate in this respect.

Diallyl sulfone adds halogens readily, in contrast to divinyl sulfone. It, likewise, forms a cyclic compound when treated with sodium hydroxide, presumably by rearrangement to β,β'-dimethyl divinyl sulfone (2).



Another class of unsaturated sulfones has been prepared by the Diels-Alder reaction of dienes with sulfur dioxide (2,13). These sulfones isomerize under the influence of ultra-violet light or base. The oxidation of substituted thiophenes also leads to sulfones of this type (14,15).





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THE SOMMELET REACTION

Reported by Harry N. Cripps March 10, 1950

Benzyl chloride and hexamethylenetetramine react in chloroform solution to give a well defined quaternary salt. Sommelet (12) discovered that this quaternary salt, when heated in aqueous solution, produced benzaldehyde in good yield.

Recently Angyal and Rossack (1,2) have investigated the Sommelet reaction further. Their chief objection to the original mechanism was a protonic shift, and they felt that the hexamine performed some function other than catalyzing this shift. The system, $\emptyset\text{-}CH_2\text{-}NH_2$, CH_2O and H_2O, was investigated and the following reactions were observed.

(a) $\emptyset\text{-}CH_2\text{-}NH_2 + CH_2O \rightleftarrows \emptyset\text{-}CH_2\text{-}N{=}CH_2 + H_2O$

(b) $\emptyset\text{-}CH_2\text{-}N{=}CH_2 + CH_2O + H_2O \rightarrow \emptyset\text{-}CH_2\text{-}NH\text{-}CH_3 + HCO_2H$

(c) $\emptyset\text{-}CH_2\text{-}N{=}CH_2 + HCO_2H \rightarrow \emptyset\text{-}CH_2\text{-}NH\text{-}CH_3 + CO_2$

Since the amount of carbon dioxide and formic acid formed did not account for the amount of N-methylbenzylamine isolated, the reaction mixture was analyzed for all constituents present. The analysis indicated that ammonia was formed in amounts equivalent to the benzaldehyde isolated. Therefore, the following reactions were also postulated.

(d) $\emptyset\text{-}CH_2\text{-}N{=}CH_2 + \emptyset\text{-}CH_2\text{-}NH_2 \rightarrow \emptyset\text{-}CH_2\text{-}NHCH_3 + \emptyset\text{-}CH{=}NH$

(e) $\emptyset\text{-}CH{=}NH + H_2O \rightarrow \emptyset\text{-}CHO + NH_3$

The fact that no methyl amine was isolated, indicated that a protonic shift did not occur. Reactions (a)-(e) quantitatively accounted for all of the methylbenzylamine formed. When hexamine was added to the system, the methylation of the benzylamine was reduced, and methyl amine was the main by-product of the reaction. Therefore, the Sommelet reaction can be regarded as the simultaneous occurrence of the following reactions:

(f) $\emptyset\text{-}CH_2\text{-}NH_2 \rightarrow \emptyset\text{-}CH{=}NH + H_2$

(g) $\emptyset\text{-}CH{=}NH \rightarrow \emptyset\text{-}CHO + NH_3$

(h) $CH_2{=}NH + H_2 \rightarrow CH_3\text{-}NH_2$

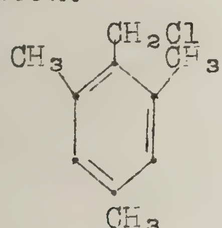
Angyal and Rassack point out that the actual reactant in reaction (h) may not be methylimine, but rather any of the many intermediate products possible from the hydrolysis of hexamine. Sommelet (3,4) later came to the above conclusions also. Unfortunately, the papers describing his conclusions were not abstracted, and therefore did not receive wide attention.

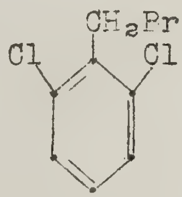
Since the methylation of benzylamine is a competing reaction, the yield of benzaldehyde could be increased by the dropwise addition of benzyl chloride to a large excess of a boiling hexamine solution. Benzaldehyde can also be formed from N-methylbenzylamine and dibenzylamine and formaldehyde (1,5). The addition of hexamine to the reaction mixture increases the yield in each case. Tribenzylamine cannot be converted to benzaldehyde in this manner (5).

The Sommelet reaction is general for arylmethylhalides providing that at least one of the positions <u>ortho</u> to the halomethyl group is unsubstituted (6). By this method, <u>o</u>-, <u>m</u>-, and <u>p</u>-bromobenzaldehydes were prepared from the corresponding bromobenzyl bromides in 47, 69 and 73 per cent yields respectively (6). Graymore (7) prepared <u>p</u>-nitro and <u>m</u>-methyl benzaldehyde in unspecified yields. Using a special procedure, <u>o</u>-iodobenzaldehyde can be prepared in 76 per cent yield (6). 1-naphthaldehyde can be prepared in 68 per cent yield (8).

Wood et al. (9) have prepared <u>p</u>- and <u>m</u>-aromatic dialdehydes from the corresponding chloromethyl compounds. In each case one position <u>ortho</u> to each chloromethyl group was unsubstituted. The reaction was not applicable to the preparation of <u>o</u>-dialdehydes.

The Sommelet reaction fails when both positions <u>ortho</u> to the halomethyl group are substituted. (I-IV) did not produce aldehydes (7,10), but the corresponding methyleneamines and amines could be isolated.


(I)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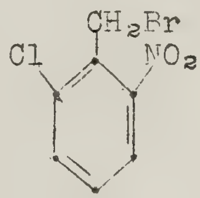
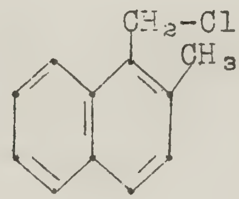

(III)


(IV)

The failure of the above compounds to produce aldehydes, gives additional support to the conclusion that the Sommelet reaction is an oxidation-reduction process because Davies (11) found that 2,6-dichlorotoluene was not attacked by chromic acid in 50% H_2SO_4. This is also in accord with the fact that the Sommelet reaction is not applicable to saturated aliphatic compounds (1,6).

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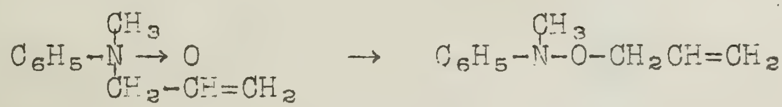
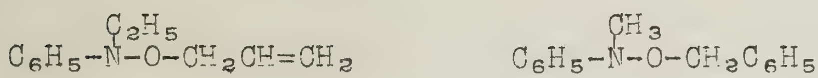
REARRANGEMENT OF ALLYL GROUPS IN DYAD SYSTEMS

Reported by Joseph A. Fuller   March 10, 1950

The Claisen rearrangement of allyl ethers of phenols or thiophenols and the rearrangement of allylthiocyanate involve α,γ migrations of the allyl group. Meisenheimer (1) demonstrated α,β migrations of allyl groups. When allylmethylaniline oxide (I) is heated with aqueous sodium hydroxide, o-allyl-N-methyl-N-phenylhydroxylamine (II) is produced in high yield. Allylethylaniline oxide and benzylmethylaniline oxide rearrange to give compounds III and IV respectively. No conclusion was reached concerning the mechanism.

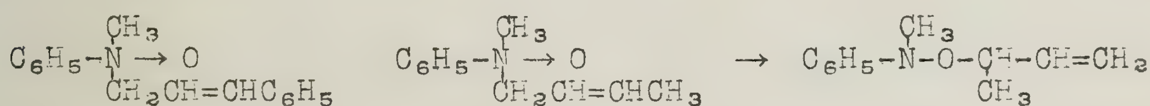


I   II



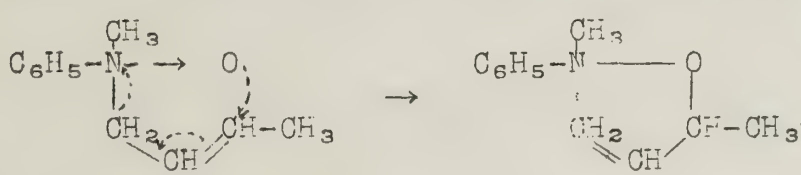
III   IV

Cope and Kleinschmidt (3) investigated the rearrangement in an effort to determine whether chain inversion occurred. Cinnamylmethylaniline oxide (V) and crotylmethylaniline oxide (VI) were examined. No pure substance could be isolated when V was heated with aqueous alkali. VI, however, gave good yields of the hydroxylamine derivative VII, thus indicating inversion of the migrating group.



V   VI   VII

An ionic mechanism seemed improbable since only one product was isolated. It also appeared that the alkali served only to free the amine oxide from its salts. The following mechanism was proposed:



Meisenheimer (2) reported that allyldimethyl- and allyldiethylamine oxides did not isomerize when heated with alkali. Reasoning that the greater tendency of the alkylamine oxides to form hydrates might interfere with rearrangement, Cope and Towle (4) investigated several allyldialkylamine oxides under conditions which did not favor hydrate formation. Rearrangement occurred

in each case as summarized in Table I. The fact that these rearrangements took place in the absence of a catalyst indicates that the role of the alkali in the previous study was correctly interpreted.

Table I

Amine Oxide	% Rearrangement
Allyldimethyl	51%
Allyldiethyl	59%
Allyldi-n-propyl	80%
Allyldiisopropyl	67%
Allyldi-n-hexyl	68%
Benzyldimethyl	61%

More recently Cope and co-workers (5) have examined some sulfur-oxygen systems for susceptibility to the rearrangement. Allyl phenyl sulfoxide, allyl phenyl sulfone and allyl vinyl sulfone could not be induced to rearrange. It had previously been shown (6) that α-phenylethyl p-toluenesulfinate (VIII) isomerizes to α-phenylethyl p-tolyl sulfone (IX) on standing, by an ionic mechanism. Cope obtained allyl phenyl sulfone (XI) in 70% yield by heating allyl benzenesulfinate (X).

$$\underset{\text{VIII}}{C_6H_5-\underset{CH_3}{CH}-O-\underset{\overset{\downarrow}{O}}{S}-C_6H_4CH_3} \rightarrow \underset{\text{IX}}{C_6H_5-\underset{CH_3}{CH}-\overset{\overset{O}{\uparrow}}{\underset{\overset{\downarrow}{O}}{S}}-C_6H_4CH_3}$$

$$\underset{\text{X}}{CH_2{=}CHCH_2-O-\underset{\overset{\downarrow}{O}}{S}-C_6H_5} \rightarrow \underset{\text{XI}}{CH_2{=}CHCH_2-\overset{\overset{O}{\uparrow}}{\underset{\overset{\downarrow}{O}}{S}}-C_6H_5}$$

When crotyl benzenesulfinate (XII) or α-methylallyl benzenesulfinate (XIII) is heated in an inert solvent, the product is crotyl phenyl sulfone (XIV) which indicates that the mechanism is probably not the same as that for the amine oxide rearrangement.

$$\underset{\text{XII}}{CH_3CH{=}CHCH_2-O-\underset{\overset{\downarrow}{O}}{S}-C_6H_5} \rightarrow \underset{\text{XIV}}{CH_3CH{=}CHCH_2-\overset{\overset{O}{\uparrow}}{\underset{\overset{\downarrow}{O}}{S}}-C_6H_5} \leftarrow \underset{\text{XIII}}{CH_2{=}CH\underset{CH_3}{CH}-O-\underset{\overset{\downarrow}{O}}{S}-C_6H_5}$$

The sulfides corresponding to XII and XIII were prepared and found to be physically distinct. The sulfones obtained by oxidation of the sulfides had the same infrared absorption spectra. The main product of hydrogenation of both sulfones was n-butyl

phenyl sulfone. Comparison of the absorption spectra showed that the sulfones obtained by oxidation were actually mixtures containing 90% crotyl phenyl sulfone and 10% of the isomeric sulfone.

The authors reach no definite conclusion but indicate that the mechanism is probably ionic. This view is supported by the fact that an equilibrium mixture of the two isomeric butenyl bromides contains over 80% crotyl bromide (7).

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NEW REACTIONS OF UREA

Reported by Franklin E. Mumford March 10, 1950

Urea is probably most accurately represented as a resonating zwitterion (1).

$$\mathrm{H{:}\ddot{N}{::}\underset{NH_3^{\oplus}}{C}{:}\ddot{O}{:}^{\ominus}} \leftrightarrow \mathrm{H{:}\overset{\ominus}{\ddot{N}}{:}\overset{\oplus}{\underset{NH_3^{\oplus}}{C}}{:}\ddot{O}{:}^{\ominus}}$$

The carbamide and amino-imino structure can also be assigned to the urea molecule, but on the basis of diamagnetic susceptibility measurements the resonating zwitterion appears more accurate. This same type of measurement has shown that the amino-imino structure is present in N-monosubstituted ureas, while the carbamide structure occurs in tetra substituted urea molecules.

Urea has been used extensively in the preparation of polymers which are useful as adhesives, coatings, binders, lacquers, shellacs, etc. (2,3,4). However, the present discussion shall concern only non-polymeric reactions.

<u>Reactions with Alcohols</u>: Monofunctional alcohols give up to 90% yield of the corresponding urethan when heated in the presence of urea with heavy metal salts of weak organic acids, stannic chloride, or cobalt chloride as catalysts (5).

$$\text{A)}\quad \mathrm{ROH + H_2N\overset{O}{\overset{\|}{C}}NH_2 \xrightarrow[\Delta]{cat.} RO\overset{O}{\overset{\|}{C}}NH_2 + NH_3}$$

In the presence of mineral acids or salts of these acids no urethan is formed, but instead an iminodicarboxylic acid, apparently through loss of ammonia from two molecules of urethan.

$$\text{B)}\quad \mathrm{2\ RO\overset{O}{\overset{\|}{C}}NH_2 \longrightarrow RO\overset{O}{\overset{\|}{C}}NH\overset{O}{\overset{\|}{C}}OR + NH_3}$$

1,2 glycols will form the diurethan or dihydro oxazole derivative depending upon the conditions used.

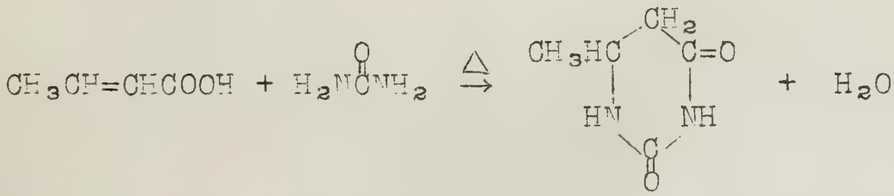
$$\text{C)}\quad \mathrm{\begin{array}{l}CH_2OH\\ CH_2OH\end{array}\quad 2\ H_2N\overset{O}{\overset{\|}{C}}NH_2 \xrightarrow[\substack{Mn(OAc)_2\\ 3\ hrs.}]{135\text{-}55^{\circ}} \begin{array}{l}CH_2O\overset{O}{\overset{\|}{C}}NH_2\\ |\\ CH_2O\overset{O}{\overset{\|}{C}}NH_2\end{array} + 2\ NH_3}$$

$$\downarrow\Delta$$

$$\text{D)}\quad \mathrm{\begin{array}{l}CH_2OH\\ CH_2OH\end{array}\quad H_2N\overset{O}{\overset{\|}{C}}NH_2 \xrightarrow[5\ hrs.]{150\text{-}5^{\circ}} \begin{array}{l}CH_2\text{-}O\\ |\\ CH_2\text{-}NH\end{array}\!\!\!\!\!\!\!>C{=}O + CO_2 + NH_3}$$

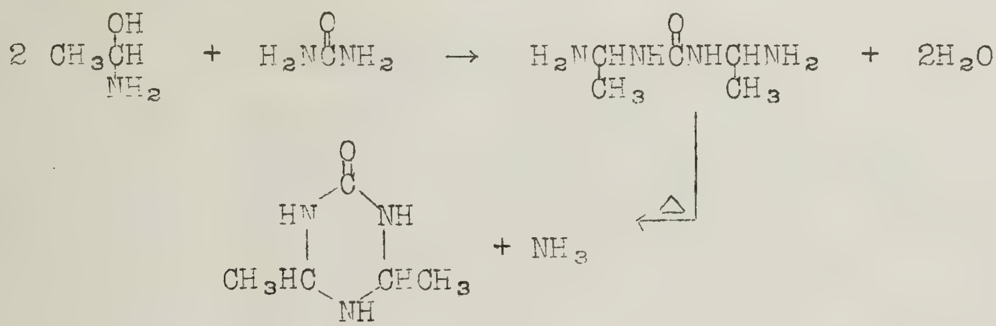
Ring formation through an intramolecular reaction does not occur in the case of the 1,3 glycols. The mono and diurethans are stable, and either may be easily prepared.

Reactions with α,β-unsaturated Acids and Aldehydes: Six-membered rings are formed when urea is heated with α,β-unsaturated acids or aldehydes (6). Thus 6-methyl hydrouracil may be synthesized from crotonic acid and urea.

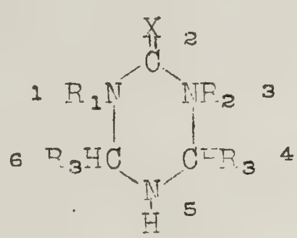
E) 

Thiourea and guanidine will react in the same manner to furnish analogous compounds.

Reactions with Aldehyde-ammonia: Moist acetaldehyde-ammonia and urea react at room temperature to give N,N'-bis (1-aminoethyl) urea. This compound loses ammonia readily, even at the boiling point of ether, to form 4,6-dimethyltetrahydro-2(1-H)-s-triazone (7,8).

F) 

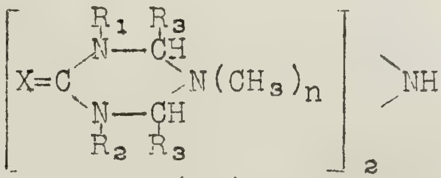
Substitution of urea by thiourea, guanidine, and N,N' disubstituted ureas gives compounds of type (I). Aliphatic amines may be substituted for ammonia in which case the 5-nitrogen will be substituted.



(I)

Formaldehyde (7,9) cannot be used as the aldehyde when ammonia is present as hexamethylene tetramine is formed. However, when amines are used, formaldehyde reacts to give 5-substituted tetrahydro-2(1-H)-s-triazones.

When a diamine is used the 5-substituted tetrahydro-2(1-H)-s-triazone obtained loses ammonia on heating to yield compounds of type (II).



(II)

Reactions with Primary Aliphatic Amines: N-methyl urea may be prepared by heating methylamine hydrochloride and urea in an aqueous solution (10,12). The symmetrical dimethylurea is obtained in a similar reaction by employing pressure and higher temperatures. Other primary amines react to give alkyl ureas (11).

Further work is being carried out by A. M. Paquin on the reactions of urea, so more, useful reactions may be expected.

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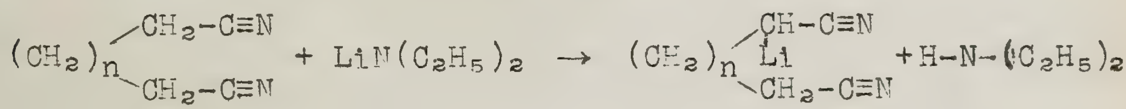
CONDENSATIONS EFFECTED BY ALKALI AMIDES

Reported by George P. Speranza March 10, 1950

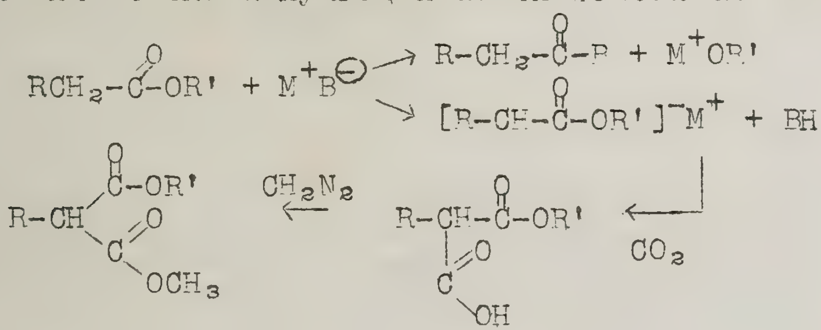
The reactions below (1) illustrate the ability of the alkali amides to replace the active hydrogen, to behave as strong bases and to attack organic compounds in a selective manner. Recently (2) it has been shown that these compounds behave as excellent condensing agents in ester condensations.

a) $R-C\equiv CH + NaNH_2 \rightarrow R-C\equiv CNa$

b) $RCHX-CH_2X + 3NaNH_2 \rightarrow R-C\equiv C-Na$

c) 

When such a basic reagent reacts with an ester, the ester may be attacked in two different positions (3), at the carbonyl carbon and at the α-hydrogen as indicated in the following scheme.



M = Na, K, MgBr
B = OC_2H_5, NH_2, $(C_6H_5)_3C^-$ etc.

If B^- is the amide ion (from sodium amide) both (a), the amide of the starting ester and (b), the ester anion are formed. However, when the larger base, sodium triphenylmethide is used in condensations apparently only α-hydrogen attack occurs (4).

The yields of β-ketoesters using lithium amide (5) as the condensing agent were considerably lower than those reported previously using sodium amide (6) to effect the same condensations. Pauling (7) has pointed out that the alkali metals decrease in electronegativity with increasing atomic weight. Consequently, in the ion pairs $Li^+NH_2^-$ and $Na^+NH_2^-$ the amide portion of sodium amide is more electronegative than that of lithium amide. This type of reaction has been carried out (8) using caesium and rubidium carbonates whereas the conversions did not take place with lithium carbonate.

The α-hydrogen of the ester was attacked by the following reagents with decreasing ease (5), Table I. Attack on the

$$LiN[CH-(CH_3)_2]_2 > LiN-(C_2H_5)_2 > LiN\begin{matrix} CH_3 \\ C_6H_5 \end{matrix}$$

carbonyl carbon occurred most readily with lithium N-methyl N-phenylamide. Similarly diisopropylaminomagnesium bromide (2) (Hauser's recommendation) has been found to be a more suitable condensing agent than diethylaminomagnesium bromide. With dicyclohexylaminomagnesium bromide and di-n-butylaminomagnesium bromide no amides were formed but the yields of the selfcondensed esters were lowered.

These results indicate that as the complexity of the basic reagent is increased, the α-hydrogen reaction of an ester is favored over the reaction at the carbonyl carbon. Mesitylmagnesium bromide (9), sodium and potassium triphenylmethides (10) react with the α-hydrogen of ethyl i-valerate or ethyl i-butyrate whereas methyl or ethylmagnesium bromides and sodium amide (3) appear to react mainly at the carbonyl carbon of the ester.

The bases were prepared in the following manner:

$$C_2H_5MgBr + [(CH_3)_2CH]_2NH \rightarrow C_2H_6 + [(CH_3)_2-CH]_2-N-MgBr$$

or

$$C_6H_5Li + (C_2H_5)_2N-H \rightarrow C_6H_6 + (C_2H_5)_2-N-Li$$

The faster rate of self-condensation of the ester in the presence of the magnesium reagent appears to be the result of the greater formation of the coordination complex (11) between the magnesium enolate and the ester as represented below in the second step; this allows the α-carbon of the enolate to approach readily the carbonyl carbon of the ester with which it condenses.

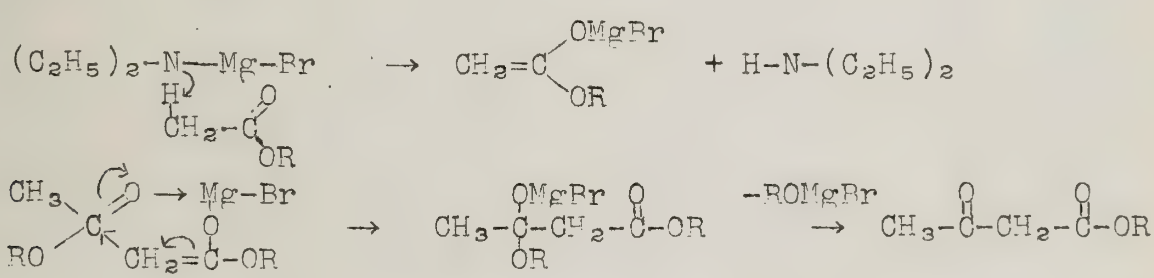


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TABLE I

Reactions of Esters with Alkali Amides

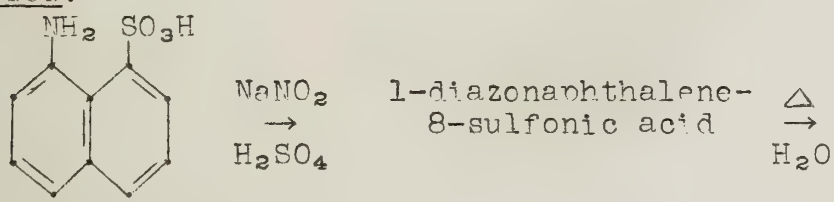
Ester	Base	Products Isolated	Yield	Ref.
Ethyl Propionate	$LiN-(C_2H_5)_2$	$C_2H_5-\overset{O}{\overset{\|}{C}}-C_2H_5$	20	5
	$LiN-[CH-(CH_3)_2]_2$	$CH_3-CH_2-\overset{O}{\overset{\|}{C}}-\overset{CH_3}{\overset{\vert}{C}H}-\overset{O}{\overset{\|}{C}}-OC_2H_5$	21.3	5
	$LiN\begin{matrix}CH_3\\C_6H_5\end{matrix}$	$CH_3-CH_2-\overset{O}{\overset{\|}{C}}-\overset{CH_3}{\overset{\vert}{C}H}-\overset{O}{\overset{\|}{C}}-OC_2H_5$	trace	5
		N-methyl-N-phenylpropionamide	57	5
	$XMg-N-[CH-(CH_3)_2]_2$	$CH_3CH_2-\overset{O}{\overset{\|}{C}}-\overset{CH_3}{\overset{\vert}{C}H}-\overset{O}{\overset{\|}{C}}-OC_2H_5$	73	2
	$XMg-N-(C_2H_5)_2$	"	76	11
Ethyl Isobutyrate	$LiN-(C_2H_5)_2$	$(CH_3)_2CH-\overset{O}{\overset{\|}{C}}-CH-(CH_3)_2$	16	5
	$LiN-(CH-(CH_3)_2]_2$	$(CH_3)_2CH-\overset{O}{\overset{\|}{C}}-\underset{CH_3}{\overset{CH_3}{C}}-\overset{O}{\overset{\|}{C}}-OC_2H_5$	49.3	5
	$BrMg-(CH-(CH_3)_2]_2$	"	55.0	2
Ethyl Isovalerate	$LiN-(C_2H_5)_2$	$(CH_3)_2-CH-CH_2-\overset{O}{\overset{\|}{C}}-CH_2-CH(CH_3)_2$	46.6	5
	$BrMg-N-[CH(CH_3)_2]_2$	N,N'diethylisovaleramide	6.6	5
		$CH_3-\underset{CH_3}{\underset{\vert}{C}H}-CH_2-\overset{O}{\overset{\|}{C}}-\underset{CH-(CH_3)_2}{\underset{\vert}{C}H}-\overset{O}{\overset{\|}{C}}-OC_2H_5$	71	2
Tert-butylacetate	$LiN-(C_2H_5)_2$	$CH_3-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-O-\underline{t}-butyl$	58.5	5
	$BrMg-N-(C_2H_5)_2$	"	55	11
Methyl laurate	$BrMg-N-[CH-(CH_3)_2]_2$	Methyl α-lauryl-laurate	92	2
Ethyl pelargonate	$LiN-(C_2H_5)_2$	Di-n-octyl ketone	44.1	5

SULTONES

Reported by Henry C. Geller   March 17, 1950

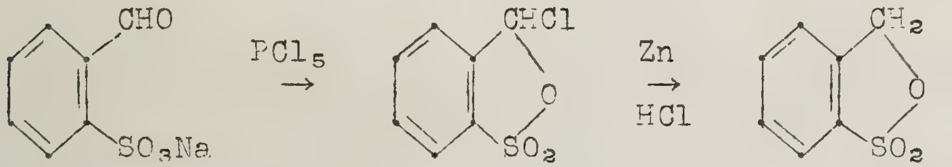
Sultones, the internal esters of hydroxysulfonic acids, are named and indexed as derivatives of the corresponding hydroxysulfonic acid, e.g. $\underset{\text{O}\text{———————}\text{SO}_2}{\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2}$ = 4-hydroxybutane-1-sulfonic acid sultone (1). However, certain trivial names persist in the literature.

Syntheses:

A. 

(2,3)

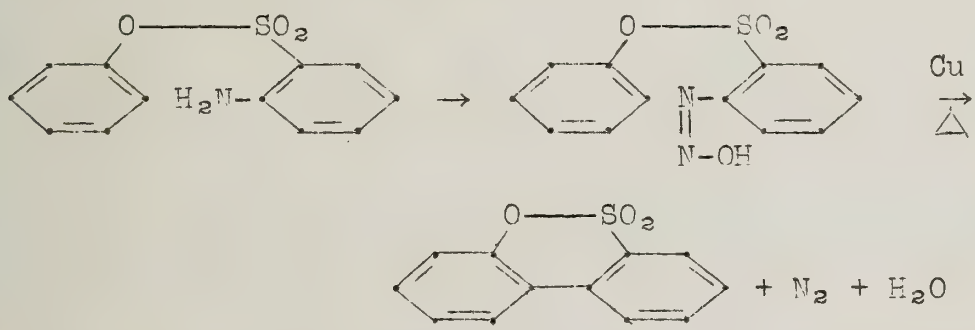
"Naphthasultone"

B. 

(4)

"Tolylsultone"

C. Diphenyl type sultones are prepared by a method similar in principle to the Pschorr phenanthrene synthesis:(5):

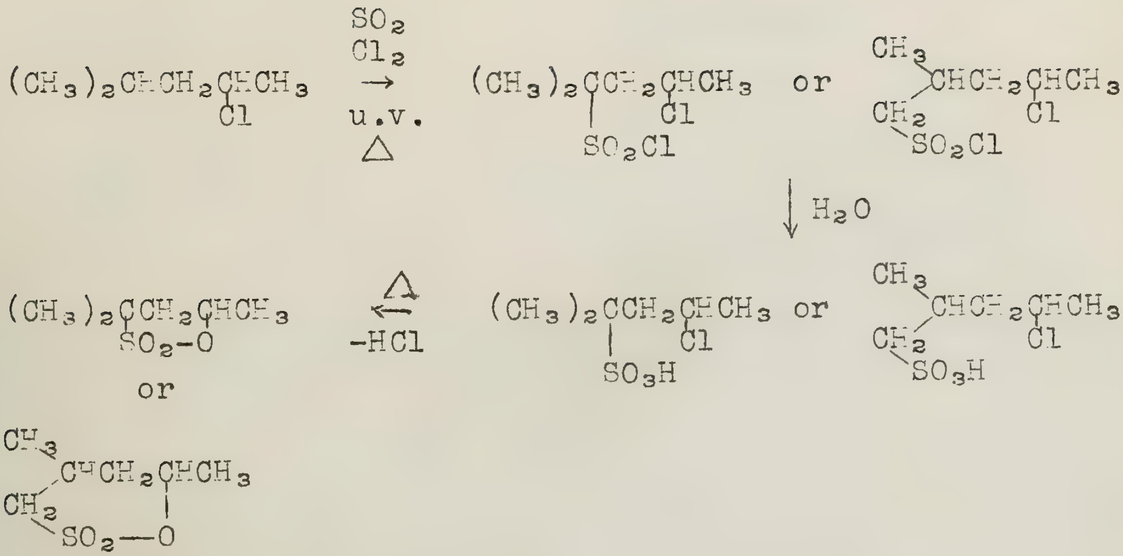


The first purely aliphatic sultone, an octanesultone, was reported in 1929, but the structure was not definitely determined (6). On the other hand, a sultone could not be formed from 3-hydroxy-n-octane-1-sulfonic acid (7). In 1940, the synthesis of 4-hydroxybutane-1-sulfonic acid sultone was reported (8):

D. $\underset{\text{Br}\qquad\qquad\quad\text{SO}_3\text{Na}}{\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2} \xrightarrow{\text{AgNO}_3} \underset{\text{O}\text{———————}\text{SO}_2}{\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2}$

Very recently Helberger and coworkers have adapted the Reed chlorosulfonation process to alkyl halides resulting in a new preparative method for aliphatic sultones (9):

E.



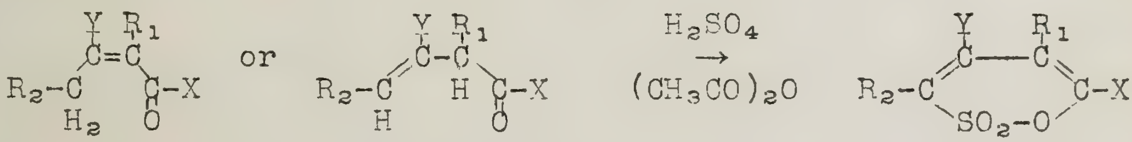
I

II

These workers consider I, a γ-sultone, the more probable in view of experimental evidence. Other sultones were prepared similarly.

An unsaturated δ-sultone was first prepared by the action of a cold mixture of concentrated sulfuric acid and acetic anhydride on either pulegone or isopulegone (10). Since then, this reaction has been extensively studied and shown to be very general for the preparation of unsaturated δ-sultones from α,β- or β,γ-unsaturated ketones substituted in the β-position:

F.



where R_1, R_2 may be H or hydrocarbon residues, but X,Y must be hydrocarbon residues. Adjacent hydrocarbon residues may be joined to form rings (11,12,13,14).

No β-sultones have ever been formed.

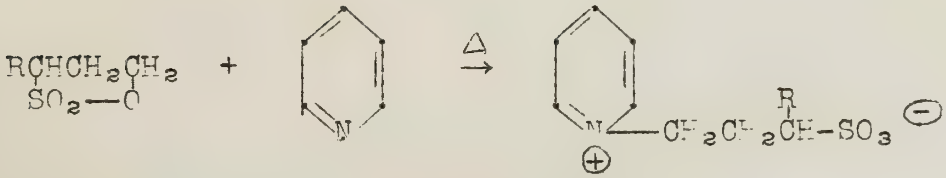
<u>Reactions</u>:

A. In general, sultones are easily hydrolyzed in boiling water.

B. Sultones will "sulfoalkylate" organic and inorganic compounds in a manner analogous to alkylation by sulfonic or sulfuric acid esters (15):

With inorganic salts, alkoxides, phenoxides, mercaptides, ammonia, aniline, pyridine, quinoline, and others:

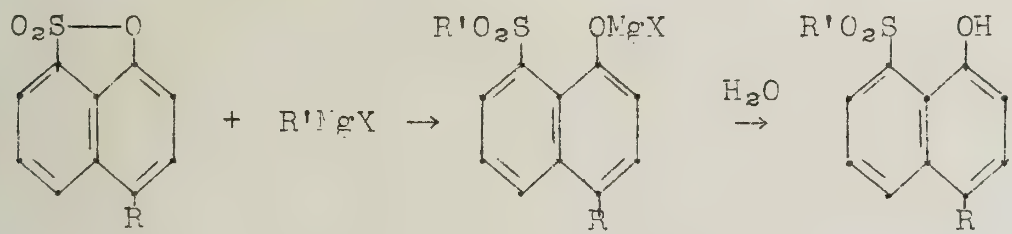
$$\underset{SO_2\text{—}O}{RCHCH_2CH_2} + C_6H_5ONa \rightarrow \underset{SO_3Na}{RCHCH_2CH_2OC_6H_5}$$



With the salts of carboxylic acids, particularly higher fatty acids, the products are ester-like compounds which are useful as surface active agents:

$$\underset{SO_2\text{—}O}{RCHCH_2CH_2} + NaO\text{-}\overset{O}{\overset{\|}{C}}\text{-}R' \xrightarrow{\Delta} \underset{SO_3Na}{RCHCH_2CH_2O\overset{O}{\overset{\|}{C}}R'}$$

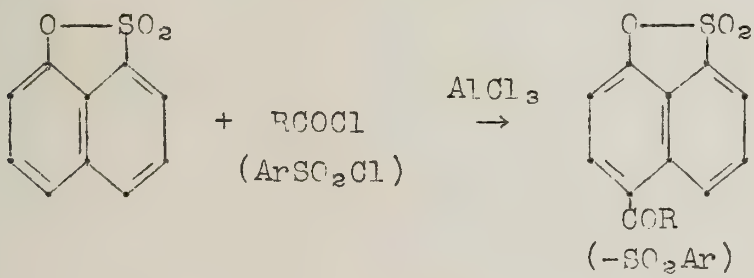
C. The reaction of Grignard reagents with naphthasultones leads to a number of new <u>peri</u>-compounds, namely hydroxyaryl-sulfones (16,17):



R = H-, CH_3-, $C_6H_5SO_2$-, CH_3<u>p</u>$C_6H_4SO_2$-

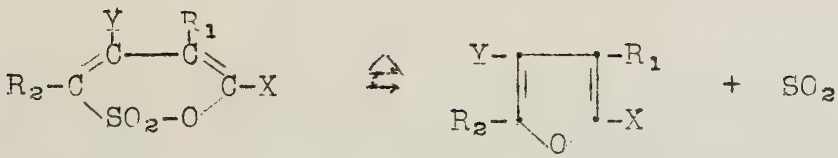
R' = CH_3-, C_2H_5-, C_6H_5-, $(CH_3)_3C$-, α-$C_{10}H_7$-

D. Acyl chlorides and aromatic sulfonyl chlorides condense with naphthasultone in a Friedel-Crafts reaction to give only the corresponding 4-keto- or 4-sulfo- derivatives (18):



<u>R</u>	<u>Yield</u>
CH_3-	74%
C_6H_5-	90
<u>Ar</u>	
CH_3<u>p</u>C_6H_4-	95

E. Pyrolysis of the previously mentioned unsaturated δ-sultones leads to a new method for synthesizing substituted furans (11,12,13,14):



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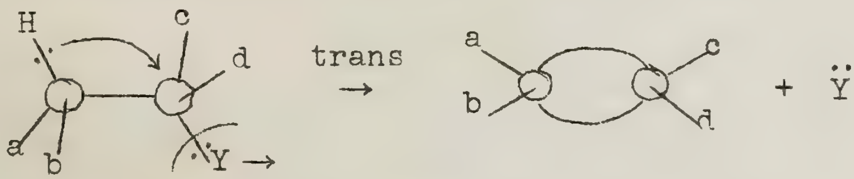
CIS ELIMINATION IN THERMAL DECOMPOSITIONS

Reported by William C. Hammann March 17, 1950

The idea of trans elimination through an E_2 reaction mechanism (1,2) has been well established. In this mechanism a nucleophilic reagent, Z, extracts a proton while an electron attracting group, Y, simultaneously separates with its previously shared electrons.

$$Z + H\text{-}CR_2\text{-}CR_2\text{-}Y \rightarrow ZH + CR_2{=}CR_2 + Y$$

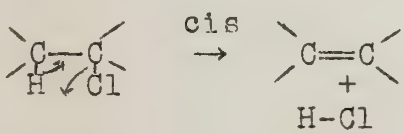
The electron pair previously shared by the proton must, if possible, enter the octet of the carbon from which Y was eliminated on the side away from Y.



Therefore, for the reaction to proceed smoothly the elimination must be trans. The stereochemical specificity of this mechanism has been valuable in configurational studies, particularly in the steroid field.

There is another type of elimination mechanism which is stereochemically specific in the cis sense. Cis elimination results from those olefin forming thermal decompositions which occur homogeneously and are unimolecular (3). This definition excludes thermal decompositions which involve surface reactions and those which are first order but proceed by a chain reaction.

The statement for the conditions for cis elimination is based on theoretical considerations concerning the transition state. It is supported by kinetic studies showing that the pyrolyses of ethyl chloride, 1,1-dichloroethane, isopropyl chloride, and t-butyl chloride proceed by a homogeneous, unimolecular reaction to give hydrogen chloride and the corresponding olefin (4,5). The transition state in these reactions is of the four center type.



The four centers must lie, suitably disposed with respect to each other, in one plane to insure minimization of the activation energy (6), and therefore cis stereochemistry is required in the reactant. This deduction appears to apply quite generally to unimolecular thermal decompositions.

Chemical evidence for the stereochemical specificity of this type of reaction is obtained from studies on the mechanism of the Chugaev xanthate reaction (7,8,9). In this reaction the transition state is believed to involve a transitory six-membered ring.

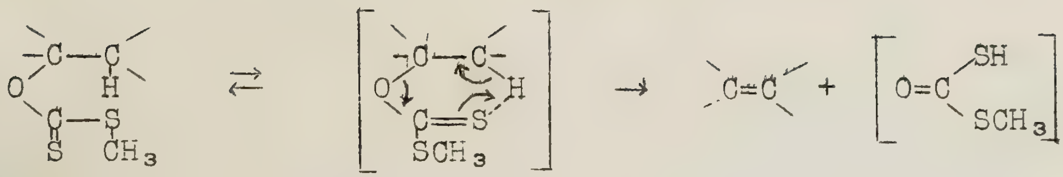
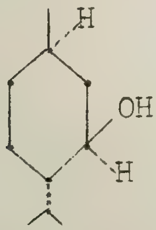
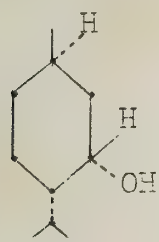
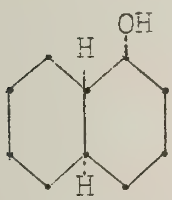
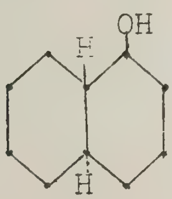
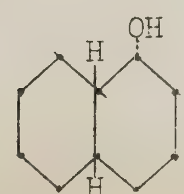
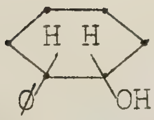
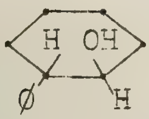


TABLE 1

Methyl xanthate from	Relation of H to Bridgehead OH	Elimination % Towards Bridgehead	Elimination % Away from Bridgehead	Ref.
I.  (–)-Menthol	cis	70	30	8
II.  (+)-neoMenthol	trans	20	80	8
III.  trans-α-Decalol (m.p. 49)	trans	20	80	8
IV.  trans-α-Decalol (m.p. 63)	cis	80	20	8
V.  cis-α-Decalol (m.p. 93)	trans	10	90	8

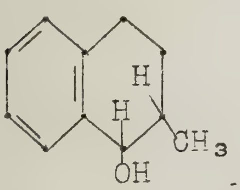
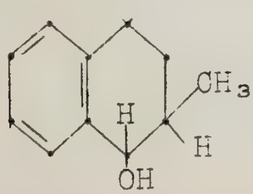
VI.  cis-2-Phenylcyclohexanol	trans	0 (7	100 93)*	9
VII.  trans-2-Phenylcyclohexanol	cis	88 (87	12 13)*	9

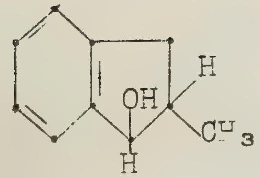
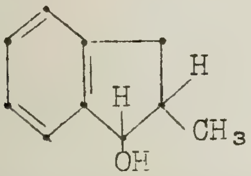
*decomposition of acetate.

The data in Tables 1 and 2 on the decomposition of xanthates can be best explained by the concept of cis elimination. Cis elimination occurs preferentially towards the bridgehead because resonance stabilization by hyperconjugation of the resulting olefin is greater in that direction.

The thermal decomposition of acetates is believed to proceed by a mechanism analagous to that of the xanthates. A kinetic study of the decomposition of t-butyl acetate indicates that in this case the reaction is unimolecular (10). The results of a recent stereochemical investigation of the reaction are summarized in Table 2 (9).

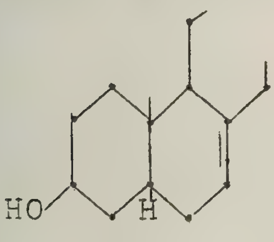
TABLE 2

Alcohol	Decomposition of Acetate		Decomp. of Xanthate
	Elimination %	Temp.	Elimination % at 98°C.
VI and VII	see Table 1.		
VIII.  cis-2-Methyl-1-tetralol	40 product was 2-methyl-naphthalene	550°	3
IX.  trans-2-Methyl-1-tetralol	85	550°	95

X. 	93	500°	82
trans-2-Methyl-1-indanol			
XI. 	93	650°	20
cis-2-Methyl-1-indanol			

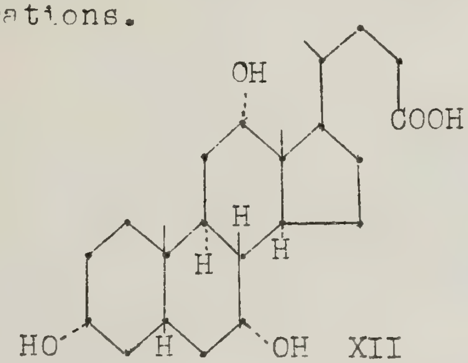
In the decomposition of acetates the data in Table 2 indicates that while <u>cis</u> elimination is preferred some other mechanism of elimination guides the reaction when <u>cis</u> elimination is not possible. A kinetic study would be of value to determine whether the mechanism is unimolecular only in the first case.

Examples of <u>cis</u> elimination have been found in the steroid field. The pyrolysis of cholic acid (XII) gives "α"-cholatrienic acid which must be formulated as XIII since it is easily hydrogenated to cholanic acid (11). Trans dehydration of cholic acid in the presence of acid catalysts gives the Δ^7 acid which cannot be easily hydrogenated. This behavior is characterisitc of 7(8), 8(9), or 8(14) unsaturations.



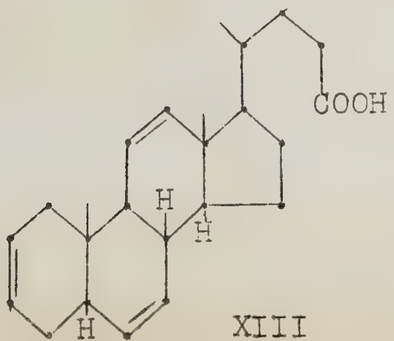
difficultly hydrogenated

acid ←



XII

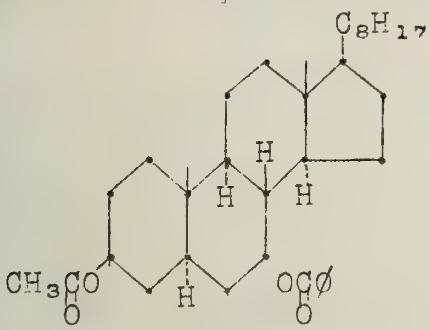
pyrolysis →



XIII

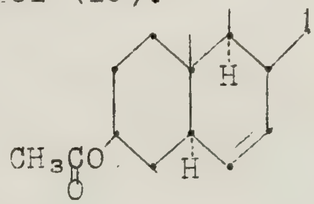
$\xrightarrow[\text{easy}]{3H_2}$ cholanic acid

The concept of cis elimination confirms Fieser's recent assignment of configuration at the 7 position in steroids of the allocholane series (12). Pyrolysis of the "β"-epimer of 3β-acetoxycholest-7-yl benzoate (XIV) gives cholest-6-en-3β-yl acetate while pyrolysis of the "α"-epimer gives cholest-7-en-3β-yl acetate. Therefore, the "β"-epimer of the diol must be cholestane-3β-7α-diol and the "α"-epimer must be cholestane-3β-7β-diol (13).

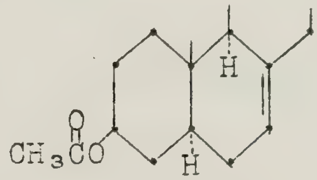


XIV

"β" epimer →



"α" epimer →



Summary:

1. Olefin forming thermal decompositions of such compounds as halides, alcohols, esters, and xanthates can be expected to proceed by cis elimination.

2. If the decomposition can be shown to be homogeneous and unimolecular, then on theoretical grounds elimination must be cis.

3. The concept of cis elimination promises to be useful in configurational studies and in fixing the position of double bonds resulting from thermal decompositions.

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FORMATION OF KETONES FROM γ-CHLOROCROTYL DERIVATIVES

Reported by Franklin E. Mange March 17, 1950

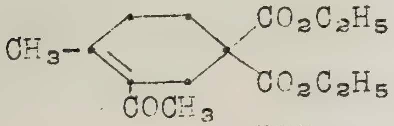
By converting certain vinyl type chlorides to the corresponding ketones, various products may be easily obtained in fair to good yields. Often these products spontaneously cyclize and they sometimes serve as useful starting materials for more difficultly obtainable substances.

Wichterle (1) observed that on washing his distillation apparatus containing the remainder of some ethyl bis(γ-chlorocrotyl) malonate (I), there was produced an evolution of hydrochloric acid. Upon investigating this phenomenon (1,2), he discovered that 1-acetyl-2-methyl-5,5-dicarbethoxy-1-cyclohexene (III) was obtained, probably through the intermediate diketone (II). Thus,

$$CH_3CCl{=}CHCH_2Cl + H_2C(CO_2C_2H_5)_2 \rightarrow (CH_3CCl{=}CHCH_2)_2C(CO_2C_2H_5)_2$$

I

$\downarrow H_2SO_4$



$\leftarrow$ $\left[(CH_3COCH_2CH_2)_2C(CO_2C_2H_5)_2 \right]$

III II

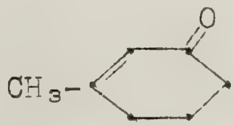
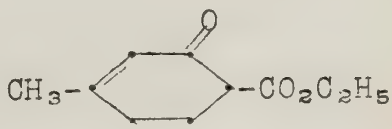
in this reaction a vinyl type chloride is converted to a ketone by the action of concentrated sulfuric acid.

By treating γ-chlorocrotyl acetic acid (IV), obtained from ethyl γ-chlorocrotyl malonate, with sulfuric acid, acetylbutyric acid (V) is obtained (2).

$$CH_3CCl{=}CHCH_2CH_2CO_2H \xrightarrow{H_2SO_4} CH_3COCH_2CH_2CH_2CO_2H$$

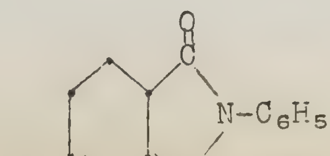
IV V

However, if ethyl (γ-chlorocrotyl) acetoacetate (VI) is treated with sulfuric acid, a mixture of 1-methyl-1-cyclohexene-3-one (VII) and 1-methyl-4-carbethoxy-1-cyclohexene-3-one (VIII) is formed (3).

$CH_3C(Cl){=}CHCH_2CH(CO_2C_2H_5)(COCH_3)$ $\rightarrow$  + 

VI VII VIII

$\swarrow C_6H_5NHNH_2$

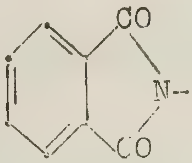
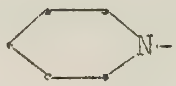


IX

This latter compound may be converted to a pyrazolone derivative (IX) by the use of phenylhydrazine.

Various mono γ-chlorocrotyl amines, amides and imines can be converted to the corresponding keto amines, amides or imines (4,5).

$$CH_3CCl{=}CHCH_2R \rightarrow CH_3COCH_2CH_2R$$

R = C_6H_5CONH-,  ,  , C_6H_5NH-, CH_3-$-NH-$

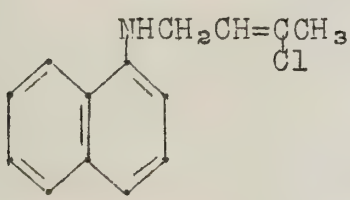
XI XII XIII

The 4-amino-2-butanone ($R{=}NH_2-$) could not be obtained directly due to resinification, but it was synthesized by hydrolyzing the phthalimido derivative (XI). It was found to be stable only in the form of a salt.

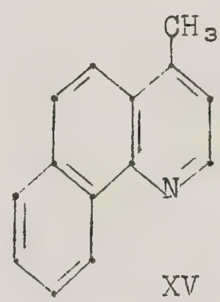
If the ethyl mercaptol is made from XI and the product oxidized and then hydrolyzed, an amino disulfone is obtained (4).

$$XI \xrightarrow{C_2H_5SH} \xrightarrow{KMnO_4} \xrightarrow{Hydrolysis} H_2NCH_2CH_2\overset{SO_2C_2H_5}{\underset{SO_2C_2H_5}{C}}CH_3$$

When $R{=}C_6H_5NH-$ (XII), besides obtaining the secondary ketoamine, some lepidine (4-methylquinoline) is obtained due to cyclization. A better yield of lepidine is obtained by carrying out the reaction at lower temperatures (40-50°) and treating the secondary ketoamine (XII) with sulfuric acid and ferric chloride. Compound XIII can be easily cyclized to 4,6-dimethylquinoline, and the α-naphthylamino derivative (XIV) is converted directly to 7,8-benzo-4-methylquinoline (XV) (5).



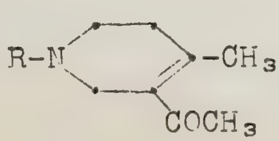
$\rightarrow$



XIV XV

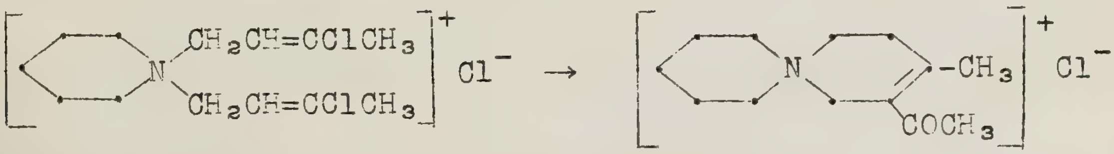
In the case of the bis (γ-chlorocrotyl) amino derivatives, 1,2,5,6-tetrahydropyridine derivatives are obtained (4).

$$R-N\begin{matrix} CH_2CH{=}CClCH_3 \\ CH_2CH{=}CClCH_3 \end{matrix} \rightarrow$$

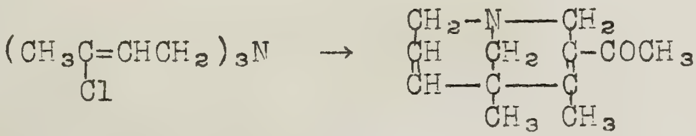


R=H, alkyl, acyl, p-toluenesulfonyl

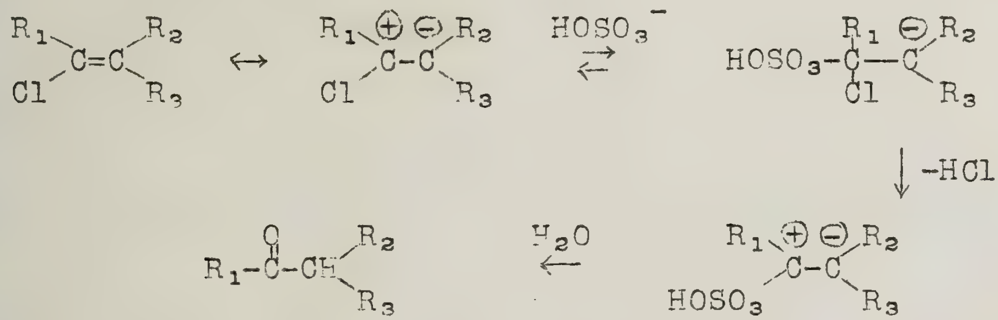
These compounds have the same ring structure as the Areca Nut alkaloids, When R is part of a ring, a nitrogen spirane is formed.



When tri (γ-chlorocrotyl) amine is treated with sulfuric acid, 3-acetyl-4,5-dimethyl-1-azabicyclo[3.3.1]nonadiene-3,6 is believed to be formed (6).



Wichterle (2) believes that the ketone is formed from the vinyl type chloride by the following mechanism.



If the inductive effects of the R groups act in such a way as to give rise to the resonance form XVI, then the reaction will proceed. The irreversible step in which hydrochloric acid is lost drives the reaction to completion.

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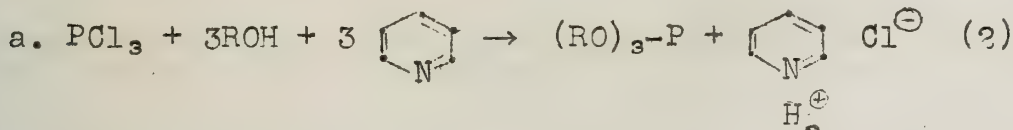
ESTERS OF PHOSPHORIC ACID

Reported by K. A. Schowalter   March 17, 1950

Recent studies in the synthesis of nucleotides have created an interest in esters of phosphoric acid and in methods of phosphorylation of alcohols. General methods for the preparation of esters containing phosphorus are reviewed briefly below:

I. Esters of Phosphorus Acid.



b. $PCl_3 + 3ROH \rightarrow [(RO)_3\text{-}P + HCl] \rightarrow (RO)_2\text{-}\overset{O}{\overset{\uparrow}{P}}\text{-}H$ (2)

c. $H_3PO_3 + RCHN_2 \rightarrow (RCH_2O)_2\text{-}\overset{O}{\overset{\uparrow}{P}}\text{-}H$ (5)

II. Esters of Phosphoric Acid.

a. $(RO)_2\text{-}\overset{O}{\overset{\uparrow}{P}}\text{-}H \xrightarrow{Cl} (RO)_2\text{-}\overset{O}{\overset{\uparrow}{P}}\text{-}Cl \xrightarrow[\text{pyridine}]{R'OH\ (ROH)} (RO)_2\text{-}\overset{O}{\overset{\uparrow}{P}}\text{-}OR'\ (OR)$ (1)

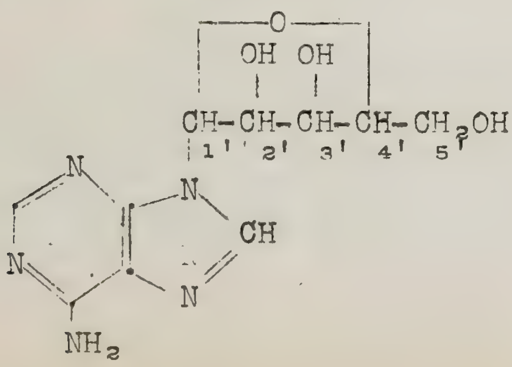
b. $(RO)_2\text{-}\overset{O}{\overset{\uparrow}{P}}\text{-}H \xrightarrow[\text{pyridine}]{Br_2,CCl_4} \xrightarrow[H_2O]{HCl} (RO)_2\text{-}\overset{O}{\overset{\uparrow}{P}}\text{-}OH$ (5)

c. $(\phi CH_2O)_2\text{-}\overset{O}{\overset{\uparrow}{P}}\text{-}Cl \xrightarrow[\text{pyridine}]{ROH} (\phi CH_2O)_2\text{-}\overset{O}{\overset{\uparrow}{P}}\text{-}OR \xrightarrow[Pd]{H_2} (HO)_2\text{-}\overset{O}{\overset{\uparrow}{P}}\text{-}OR$ (1)

III. Esters of Pyrophosphoric Acid.

$(RO)_2\text{-}\overset{O}{\overset{\uparrow}{P}}\text{-}OH \xrightarrow{Ag^{\oplus}} \xrightarrow{(RO)_2\text{-}\overset{O}{\overset{\uparrow}{P}}\text{-}Cl} (RO)_2\text{-}\overset{O}{\overset{\uparrow}{P}}\text{-}O\text{-}\overset{O}{\overset{\uparrow}{P}}\text{-}(OR)_2$ (4)

These esters are of particular importance in the synthesis of nucleotides (3) which are of wide occurrence. They consist of three basic units - a cyclic nitrogenous substance, a sugar, and a phosphoric acid unit. The cyclic nitrogenous portion is usually a purine or pyramidine and the sugar is usually d-ribose. These two together constitute the nucleoside. A typical nucleoside is adenosine, which is the nucleoside unit of the nucleotides muscle adenylic acid and adenosine triphosphate.



Adenosine

In muscle adenylic acid the above nucleoside has a simple phosphoric acid unit on the 5' carbon, whereas in other nucleotides a di-or triphosphoric acid unit exists.

R=adenosine residue

$$R-O-\overset{O}{\overset{\uparrow}{P}}-(OH)_2 \qquad R-O-\underset{OH}{\overset{O \atop \uparrow}{P}}-O-\underset{OH}{\overset{O \atop \uparrow}{P}}-OH \qquad R-O-\underset{OH}{\overset{O \atop \uparrow}{P}}-O-\underset{OH}{\overset{O \atop \uparrow}{P}}-O-\underset{OH}{\overset{O \atop \uparrow}{P}}-OH$$

muscle adenylic acid   adenosine diphosphate   adenosine triphosphate

Due to the nature of the nucleoside residue, it was necessary that the phosphoric acid unit be added under mild condition and for this reason a phosphorylation employing a dialkylchlorophosphonate was employed. It was found that dibenzylchlorophosphonate (prepared by reaction II a, where $R=\phi\cdot CH_2\cdot$) was particularly suited since the reactions went well and the benzyl groups were readily removed by hydrogenation or mild hydrolysis. Thus the monophosphate nucleotides could be readily synthesized according to the following scheme (4):

$$R'OH \xrightarrow[\text{pyridine}]{(\phi CH_2O)_2-\overset{O}{\overset{\uparrow}{P}}-Cl} R'-O-\overset{O}{\overset{\uparrow}{P}}-(OCH_2\phi)_2 \xrightarrow[\text{Pd on C.}]{H_2} R'-O-\overset{O}{\overset{\uparrow}{P}}-(OH)_2 \xrightarrow[H^{\oplus}]{\text{Hyd.}} \text{nucleotide}$$

R' Nucleoside (with 2', 3' isopropylidine group)

The di- and triphosphate nucleotides, however, imposed the problem of adding additional phosphoric units. Although this was accomplished in the case of the diphosphate compound according to the following procedure, the method was not too satisfactory (4).

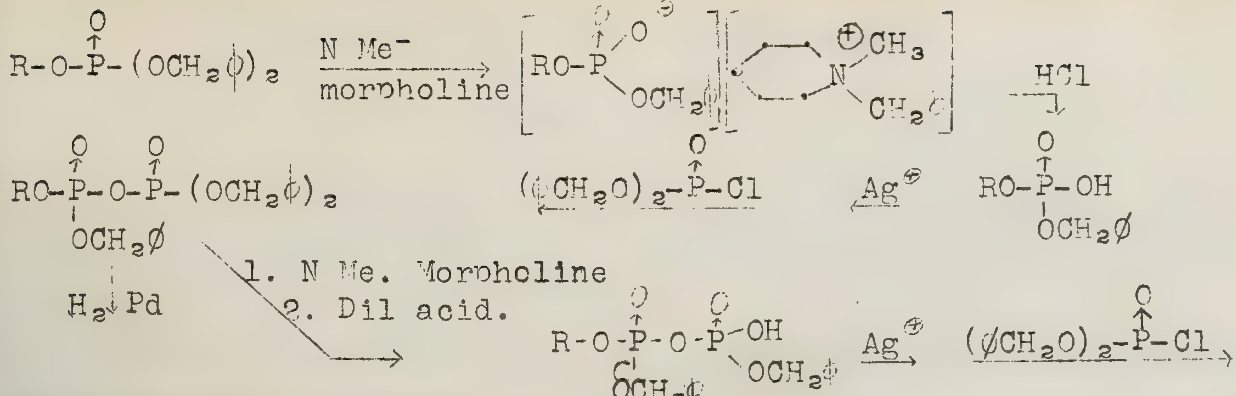
$$R'-O-\overset{O}{\overset{\uparrow}{P}}-(OCH_2\phi)_2 \xrightarrow[\text{Hyd.}]{\text{careful}} R-O-\underset{OCH_2\phi}{\overset{O \atop \uparrow}{P}}-OH \xrightarrow{Ag^{\oplus}} \xrightarrow{(\phi CH_2O)\overset{O}{\overset{\uparrow}{P}}-Cl} R-O-\underset{OCH_2\phi}{\overset{O \atop \uparrow}{P}}-O-\underset{OCH_2\phi}{\overset{O \atop \uparrow}{P}}-OCH_2\phi$$

$$\xrightarrow[\text{Pd}]{H_2} \text{adenosine diphosphate}$$

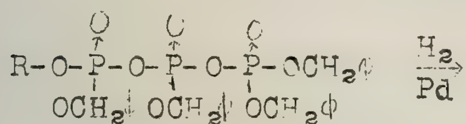
R=adenosine residue
R'=2',3' isopropylidine adenosine residue.

Recently Todd and his co-workers (7) have found that by treatment of benzyl esters of phosphorus, phosphoric and pyrophosphoric acids with a tertiary amine, such as N-methyl morpholine, a quaternary salt is formed which, when decomposed, yields the ester in whic one benzyl group has been replaced with hydrogen. Thus the di- and triphosphate nucleotides were readily synthesized according to the following scheme (6):

R=adenosine residue



Adenosine 5' diphosphate
(Identical with natural prod.)



Adenosine triphosphate
(Identical with natural product)

This monodebenzylation reaction employing N-methyl morpholine is quite general and is an excellent synthetic approach to mixed phosphorus, phosphoric and pyrophosphoric esters.

In addition to the applications of these phosphorus compounds in the synthesis of nuclcotides, other uses are briefly as follows:

1. Phosphorylation of amines to yield dialkylaminophosphonates (1)

$$(RO)_2\text{-}\overset{O}{\overset{\uparrow}{P}}\text{-Cl} + R'NH_2 \rightarrow (RO)_2\text{-}\overset{O}{\overset{\uparrow}{P}}\text{-NHR'}$$

where R'=H, ϕ, or alkyl.

2. The preparation of dialkylfluorophosphonates $(RO)_2\text{-}\overset{O}{\overset{\uparrow}{P}}\text{-F}$, many of which were prepared during the war and investigated as toxic agents (10).

3. Employment of trialkylphosphoric esters as alkylating agents for alcohols, amines and phenols (8)(9)(11).

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NITRO ALKENES--RECENT DEVELOPMENTS

Reported by Donald P. Hallada   March 24, 1950

The recent advent of availability of the lower nitro paraffins (1) and the nitro alcohols (2) has stimulated work on the nitro alkenes and related compounds. The chemistry of the nitro alkenes has previously been reviewed (3).

Methods of preparation of nitro alkenes are illustrated below.

1. Aliphatic

$$RCHO + R'CH_2NO_2 \xrightarrow{Ca(OH)_2} RCHOHCH(NO_2)R'$$

$$RCHOHCH(NO_2)R' \xrightarrow{Ac_2O} RCH(OAc)CH(NO_2)R'$$

$$RCH(OAc)CH(NO_2)R' \xrightarrow{Na_2CO_3} RCH{=}C(NO_2)R'$$

2. Aromatic

$$ArCHO + RCH_2NO_2 \xrightarrow{1^\circ\ Amine} ArCH{=}C(NO_2)R$$

Nitro alkenes are readily reduced by iron and hydrochloric acid (4). The product is either the ketoxime or ketone, depending on the amount of acid employed. Hydrogen and a nickel catalyst, however, reduced either the nitro alkene or the ketoxime to the corresponding amine, and also reduce the ketone to the corresponding alcohol (4,5). These interconversions are illustrated below.

$$RCH{=}C(NO_2)R' \xrightarrow[H_2O]{Fe,HCl} RCH_2C(R')NOH \xrightarrow[H_2O]{HCl} RCH_2COR'$$

$$RCH{=}C(NO_2)R' \xrightarrow{H_2,Ni} RCH_2CH(NH_2)R'$$

$$RCH_2C(R')NOH \xrightarrow{H_2\ Ni} RCH_2CH(NH_2)R'$$

$$RCH_2COR' \xrightarrow{Ni\ H_2} RCH_2CHOHR'$$

This series of reactions thus presents a method of performing the following transformations.

$$RCHO \rightarrow \begin{array}{c} RCH_2CH(NH_2)R' \\ \text{or} \\ RCH_2CHOHR' \end{array} \qquad \begin{array}{l} R = \text{Alkyl or Aryl} \\ \\ R' = \text{Alkyl} \end{array}$$

The use of α and β-nitro-olefins in the Friedel-Crafts reaction with aromatic hydrocarbons has been investigated (6). The reactions of the β-unsaturated nitro compounds were normal, as illustrated below.

$$CH_2{=}C(CH_3)CH_2NO_2 \xrightarrow[AlCl_3]{ArH} ArC(CH_3)_2\text{-}CH_2NO_3$$

Boron trifluoride also was used as the catalyst. Catalytic hydrogenation of the product gave the corresponding amine.

Reactions of the α-unsaturated nitro compounds were more complex.

$$(CH_3)_2C{=}CHNO_2 \xrightarrow[BF_3]{CH_3C_6H_5} \underset{\text{I}}{CH_3C_6H_4C(CH_3)_2CH_2NO_2} + \underset{\text{II}}{CH_3C_6H_4C(CH_3)_2CONHOH}$$

The α-p-tolylisobutyrohydroxamic acid (II) was probably formed by 1,4 addition to the nitro olefin to give the aci-nitro compound (III), followed by rearrangement.

$$(CH_3)_2\text{-}C{=}CHNO_2 \rightarrow \underset{\text{III}}{CH_3C_6H_4C(CH_3)_2CH{=}\overset{\overset{O}{\uparrow}}{N}\text{-}OH} \rightarrow \underset{\text{II}}{CH_3C_6H_4C(CH_3)_2\text{-}CONHOH}$$

1,2 addition, or an alternate rearrangement of (III) would explain the formation of the 1-nitro-2-p-tolyl-2-methylpropane (I).

Attempts to cause 1-nitro-2-methylprop-1-ene to react with benzene in the presence of boron trifluoride failed. The reaction occurred readily when aluminum chloride was used as the catalyst, the products being α,β-dichloroisobutyraldoxime (IV) and α-phenylisobutyrohydroxamyl chloride (V). The dichloro compound (IV) is

$$(CH_3)_2C{=}CH\text{-}NO_2 \xrightarrow[AlCl_3]{C_6H_6} \underset{\text{IV}}{(CH_3)_2C(Cl)\cdot C(Cl){=}NOH} + \underset{\text{V}}{(CH_3)_2C(C_6H_5)C(Cl){=}NOH}$$

presumably formed by addition of traces of hydrogen chloride to the nitro alkene. The phenyl derivative (V) is then formed in the expected fashion by the reaction of benzene and (IV) thereby forming more hydrogen chloride for further reaction.

Nitro alcohols have been employed in the Friedel-Crafts reaction. Benzene and 1-nitro-2-propanol reacted in the presence of aluminum chloride to give a mixture of 1,1-diphenylethane and benzaldoxime. The products are explained, assuming an initial dissociation into nitromethane and acetaldehyde.

$$NO_2CH_2CHOHCH_3 \rightarrow CH_3NO_2 + CH_3CHO$$

$$CH_3CHO \xrightarrow[AlCl_3]{C_6H_6} CH_3CH(C_6H_5)_2$$

$$CH_3NO_2 \xrightarrow[AlCl_3]{C_6H_6} C_6H_5CH{=}NOH$$

A mixture of nitromethane and benzene in the presence of aluminum chloride gave a small yield of a mixture of benzaldoxime and benzaldehyde anil. This reaction is of some interest in view of recent patents (7) which describe the use of nitro paraffins as solvents for the Friedel-Crafts reaction.

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THE EFFECT OF ISOTOPIC CARBON ON REACTION RATES

Reported by John C. Lorenz   March 24, 1950

Although it has long been recognized that the mass differences in the isotopes of various elements would lead to differences in the physical and chemical properties of compounds containing different isotopes of the same element, the first reported observation of an appreciable effect of isotope substitution on the reactivity of a carbon-carbon bond was that of Beeck *et al.* in 1948. By mass spectrographic analysis of the products of electron bombardment (1) and thermal cracking (2) these workers showed that the presence of C^{13} in the propane molecule decreased the possibility of C^{12}-C^{13} rupture by 12±1% and increased the possibility of C^{12}-C^{12} rupture by 7±0.2% as compared to the C^{12}-C^{12} rupture in the normal (all C^{12}) molecule.

This reaction was treated theoretically by Bigeleisen (3), who calculated ratios of rate constants for the following reactions by an equation developed from statistical rate theory (4).

$$C^{12}H_3\text{-}C^{12}H_2\text{-}C^{12}H_3 \xrightarrow{k_1} C^{12}H_3 + C^{12}H_2\text{-}C^{12}H_3$$

$$C^{12}H_3\text{-}C^{12}H_2\text{-}C^{13}H_3 \xrightarrow{k_2} C^{13}H_3 + C^{12}H_2\text{-}C^{12}H_3$$

$$C^{12}H_3\text{-}C^{12}H_2\text{-}C^{13}H_3 \xrightarrow{k_3} C^{12}H_3 + C^{12}H_2\text{-}C^{13}H_3$$

Examples of his results are given in Table I.

TABLE I

$T^{o}K$	$k_1/2k_2$	$k_1/2k_3$
300	1.043	1.023
800	1.024	1.004

The significant point is that the ratio $k_1/2k_3$ was calculated as greater than one while Beeck's experimental data gave a value less than one.

Yankwich and Calvin (5) observed that in the decarboxylation of mono-C^{14}-labeled malonic and bromomalonic acids the CO_2 evolved contained less than 1/2 of the C^{14} in the original acids. Their results were based on the counting of radioactive disintegrations of the dibasic acid and the CO_2 and acetic acid formed in the thermal decarboxylation of the acids. The results were reported as the ratio of the frequency of rupture of the C^{12}-C^{12} bond to the frequency of rupture of the C^{12}-C^{14} bond. For malonic acid the ratio was 1.12 and for bromomalonic 1.41.

Bigeleisen (6) subjected this reaction also to his theoretical treatment with the following results:

$$XCH\text{-}(COOH)_2 \xrightarrow{k_1} CO_2 + XCH_3COOH$$

$$XCH\begin{matrix} \diagup C^{14}OOH \\ \diagdown COOH \end{matrix} \xrightarrow{k_2} C^{14}O_2 + XCH_3COOH$$

$$XCH\begin{matrix} \diagup C^{14}OOH \\ \diagdown COOH \end{matrix} \xrightarrow{k_3} C^{12}O_2 + XCH_3C^{14}COH$$

where X equals H or Br

	Bromomalonic acid		Malonic acid	
T^oK	$k_1/2k_2$	$k_1/2k_3$	$k_1/2k_2$	$k_1/2k_3$
300	1.044	1.0063	1.042	1.0041
400	1.042	1.0037	1.041	1.0029

It will be at once observed that these values are quite inconsistent with the experimental observations of Yankwich and Calvin.

In order to check the validity of the calculations Bigeleisen and Friedman (7) measured the ratio of $C^{13}O_2$ to $C^{12}O_2$ in the gas evolved during the decarboxylation of "normal" malonic acid. Comparison of this ratio to the C^{13},C^{12} ratio of tank CO_2 showed that the ratio of reaction rates k_3/k_2 (see equations above where C^{14} is replaced by C^{13}) was equal to 1.020 as compared to a calculated value of 1.019$\pm$0.001. Thus the theoretical equations seemed to apply, at least to the case of C^{13}.

Pitzer (8) has recently made a contribution toward the resolution of these disagreements between theory and experiment. He revised the simplified model molecule to which Bigeleisen's equation is applied in such a fashion that he obtained a value of 1.14 as the ratio of the rates of breaking of C^{12}-C^{12} to the rate of breaking of C^{12}-C^{14} bonds in malonic acids. This compares favorably with the experimental value of 1.12$\pm$0.03, but, since the model used makes no distinction between malonic and bromomalonic acids, the value of 1.4$\pm$0.1 for bromomalonic acid is still unexplained.

At least three other reports have been made of appreciable isotopic effects on the rates of reaction of carbon-carbon bonds. Lindsay, McElcheran, and Thode (9) report that in the decomposition of oxalic acid into CO, CO_2 and H_2O in concentrated H_2SO_4 there is a higher rate of decomposition of oxalic acid molecules containing only C^{12} atoms over those containing C^{13} atoms. This effect is of the order of magnitude which Bigeleisen has predicted theoretically for malonic acid. Myerson and Daniels (10) have observed that the CO_2 evolved from decomposition of C^{14}-labeled urea with urease showed a decrease with time in the percentage of $C^{14}O_2$ in the evolved gas. The results imply that in this system

the C^{12}-C^{14} bond reacts more rapidly than the C^{12}-C^{12} bond. And finally, Stevens and Attree (11) found that the hydrolysis of C^{14}-labeled ethyl benzoate proceeded less rapidly than that of C^{12} ethyl benzoate. Their quantitative measurements gave the ratio of the rate of hydrolysis of unlabeled ester to labeled ester as 1.16 ± 0.017.

It is possible that certain biological processes can exhibit appreciable isotope effects in similar fashion. This has been inferred (12) from the measurements by Nier et al. (13,14) of the ratio C^{12}/C^{13} in various materials. In general the ratio is higher for carbon derived from plants, coal, etc., than for carbon from the air, rocks, etc. This would seem to indicate that living plants are able to accept, during photosyntheses, $C^{12}O_2$ at a somewhat greater proportionate rate than $C^{13}O_2$. This effect has been observed semiquantitatively during the photosynthetic uptake of CO_2-$C^{14}O_2$ mixtures by barley leaves (12,15). The effect is so pronounced that the specific activity of the atmospheric radiocarbon dioxide reaches, at one point, a figure some 1.2 times its original value under the conditions of the experiment.

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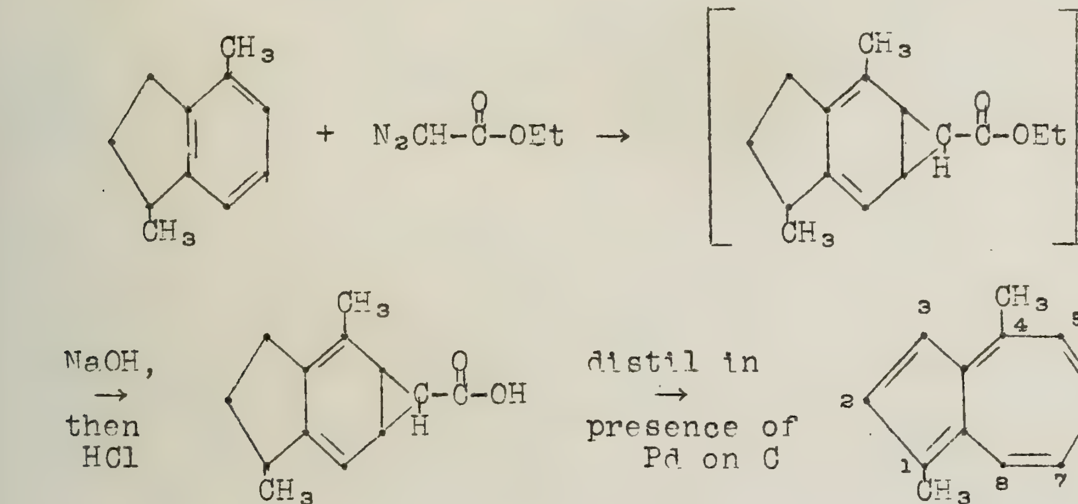
RECENT SYNTHESES IN THE AZULENE SERIES

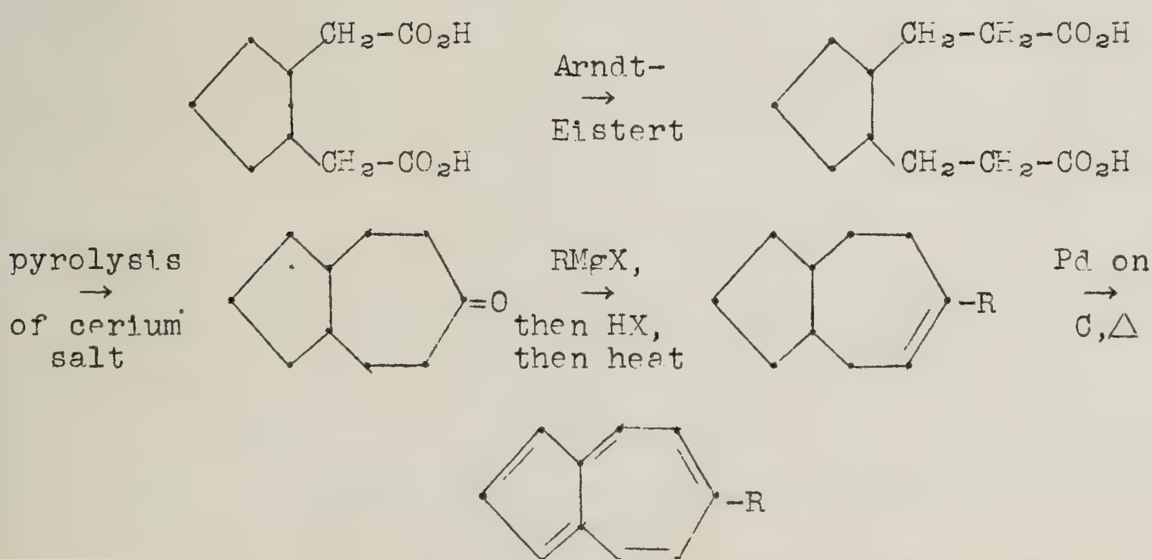
Reported by Roger W. Roeske March 24, 1950

When many sesquiterpenes are heated with sulfur or selenium, azulenes are formed. Plattner (1) obtained a compound thought to be 1,4-dimethylazulene (I) from the sesquiterpene guajol. 1,4-Dimethylazulene was synthesized and found to be identical with the azulene from guajol.



I

To aid in the structure proof of sesquiterpenes, Plattner and his co-workers undertook a systematic synthesis of alkyl-substituted azulenes (2). Some of these syntheses have been reported in a previous seminar (3). All the theoretically possible alkyl azulenes except the 6-isomer can be synthesized from the corresponding substituted hydrindenes by the diazoacetic ester method. 6-Alkyl azulenes are synthesized as follows (4).

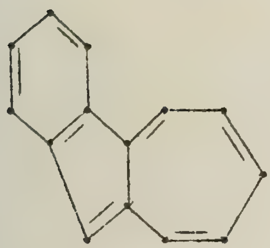


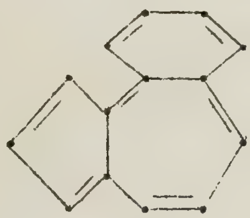
The tendency to form azulenes is evidently very great because of the aromatic character of these peculiar compounds. The five

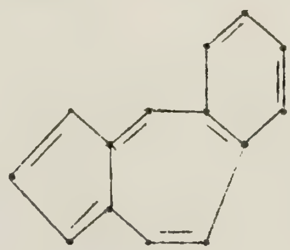
double bonds are completely conjugated. Attempted preparation of 1-phenylazulene by the diazoacetic ester method yielded only 2-phenylazulene (5). Presumably the phenyl group migrates in the last step of the synthesis.

The alkyl azulenes are blue solids or oils which form molecular compounds with picric acid and trinitrobenzene. They are soluble in 85% phosphoric acid. Alkyl substituents in the 1,3,5, and 7-positions have a bathochromic effect; they shift the color toward the blue. Alkyl substituents in the 2,4,6, and 8-positions have the opposite effect; the color is shifted toward the red. This influence of substituents is stronger in the 5-ring than in the 7-ring.

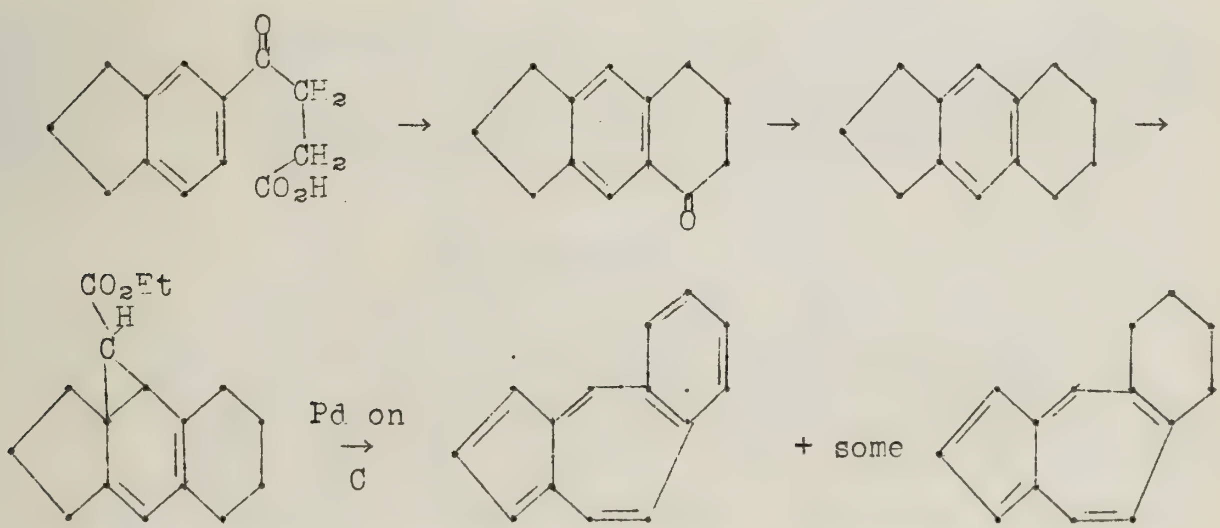
Three benzazulenes are theoretically possible.


II

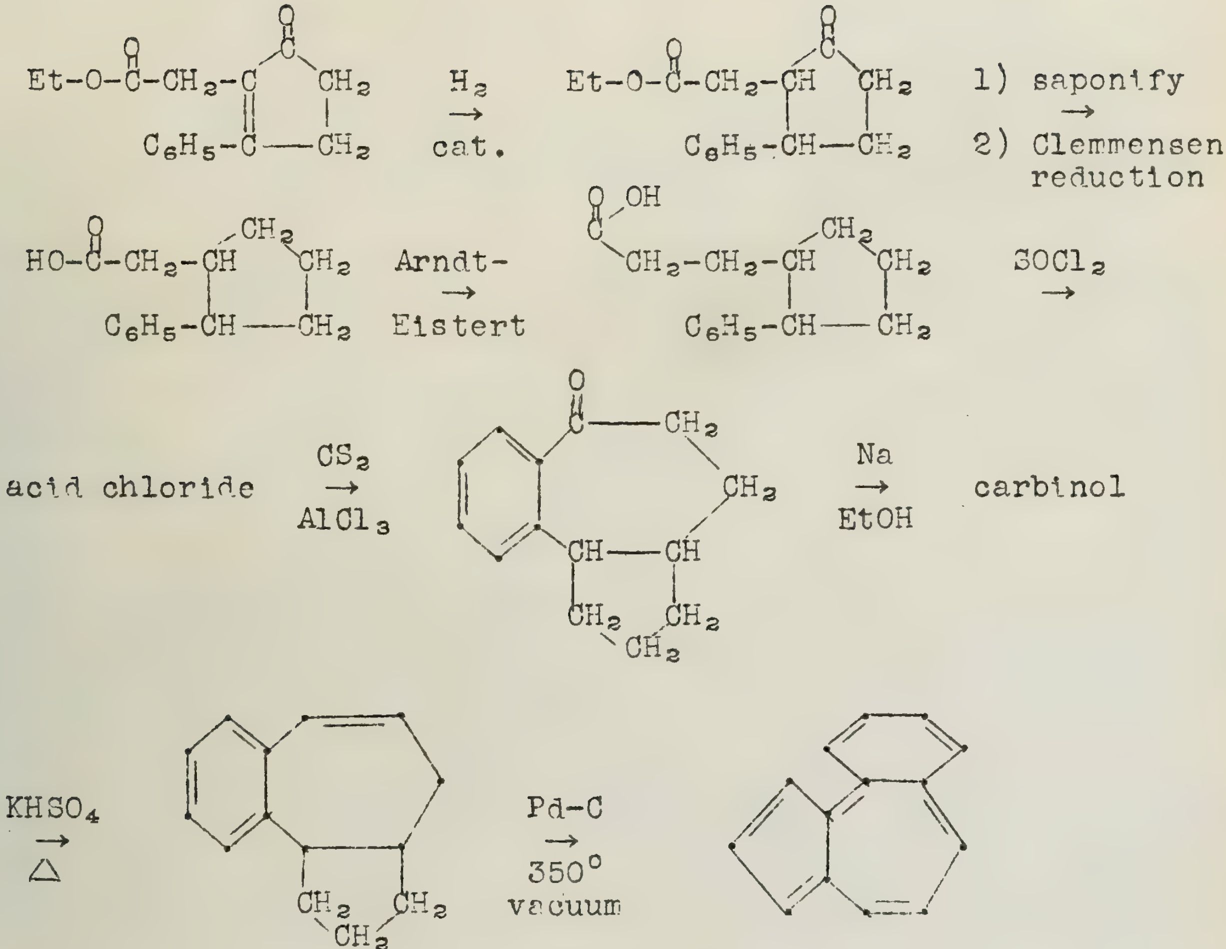

IV


III

Synthesis of II was effected by the diazoacetic ester method using fluorene as the starting material (6). Compound III was prepared in the following manner (7).



Nunn and Rapson (8) recently prepared 4,5-benzazulene (IV) and found it to be very unstable.



III

The product forms stable molecular compounds with trinitrobenzene and trinitrotoluene but cannot be obtained pure for analysis. It changes to an insoluble green substance even in an atmosphere of carbon dioxide. The effect of polarizing substituents on the stability of 4,5-benzazulene is being studied.

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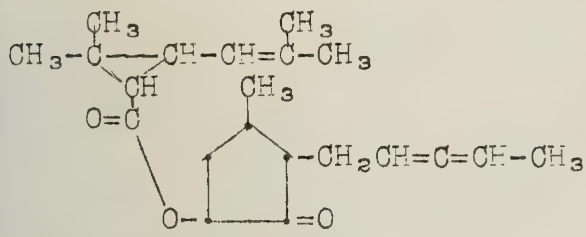
THE STRUCTURE AND SYNTHESIS OF PYRETHRINS

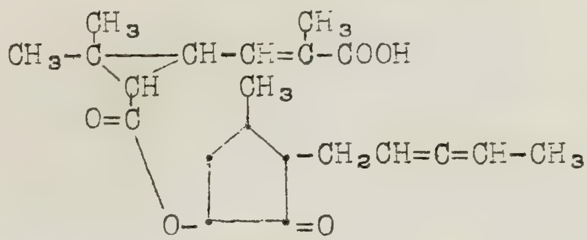
Reported by Charles H. Benton March 31, 1950

The fact that the sap of certain flowers contained compounds with insecticidal properties has been known for over a century, but it was not until 1924 that structures were proposed for the active principles by Staudinger and Ruzicka (1) (I and II).



Pyrethrin I

I



Pyrethrin II

II

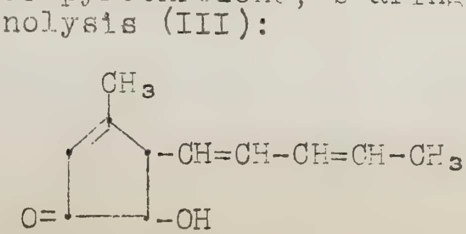
These workers synthesized the acid fragment of I, called chrysanthemum monocarboxylic acid, from 2,5-dimethyl-2,4-hexadiene and diazo-acetic ester. The structure of the alcohol portion, called pyrethrolone, was not widely accepted due to the allene side chain which has never been reported in a natural product.

With purer compounds, LaForge and Haller (2) found a discrepancy in the empirical formula of pyrethrolone. Actually there should be two less H atoms. Finding that two moles of hydrogen were readily absorbed by the compound and a third much less readily, they proposed a double bond in the 2,3-position of the nucleus.

Throughout the next few years, elucidation of the structure centered on the side chain of pyrethrolone.

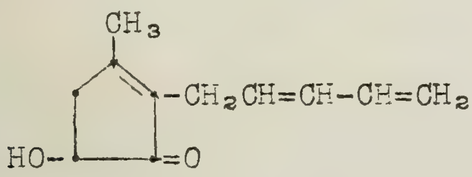
In 1942, because pyrethrolone did not form an adduct with maleic anhydride or other reactive dienophiles (3), the cumulative bond system was hesitatingly allowed to remain despite other contraindications.

Later, the same workers synthesized compounds similar to pyrethrolone, but known to contain the allene structure in the side chain and compared their ultraviolet absorption spectra with that of the natural compound. The results were interpreted to support the allene system (4). Two months later, the English group, headed by Harper and West, used ultraviolet absorption spectra to show just the opposite (5). They claimed that the side chain contained two conjugated double bonds, but that they were not in conjugation with the nuclear unsaturation. They postulated the following structure for pyrethrolone, bearing in mind that acetaldehyde is formed on ozonolysis (III):

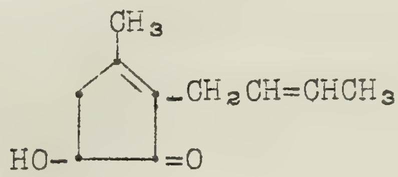


III

It was not until 1944 that LaForge's group discovered that the alcoholic fragment of the molecule was not homogeneous (6,7) and actually consisted of two substances which they named pyrethrolone (IV) and cinerolone (V) and assigned the following structures to them:

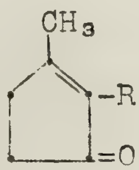


IV



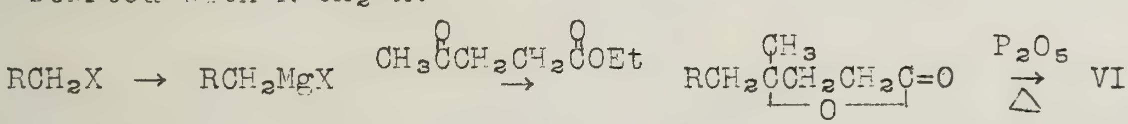
V

This same group developed a synthesis (8) of substituted ketones of the type (VI):



VI

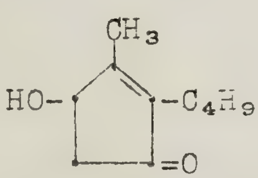
They started with $R-CH_2-X$:



The compound where R is <u>n</u>-amyl was prepared and shown to be identical with that compound prepared by reduction and hydrogenation of the natural pyrethrolone.

At this point, it is important to mention that the American workers prepared pure pyrethrins I and II and cinerins I and II (9), as the esters of cinerolone and chrysanthemum mono- and dicarboxylic acids were called, and found that the insecticidal activity was independent of the optical activity of either portion of the molecules. The order of activity was found to be pyrethrin I > cinerin I > pyrethrin II > cinerin II.

These men then synthesized VII from VI, where R is <u>n</u>-butyl, for comparison with dihydrocinerolone (10).



VII

They found that it was <u>not</u> identical with dihydrocinerolone from natural sources. Since compound VI, where R is <u>n</u>-amyl, is identical with the natural compound, it could only mean that the hydroxyl group was misplaced in the structure and should be in

position 4. These new structures fitted all the information obtainable and explained the reactivity of that group. The next step was a synthesis of this compound for comparison with that obtained from the natural series. They accomplished this (11) and proved the identity. They started with VI where R is <u>n</u>-butyl and obtained the 4-bromo derivative with N-bromosuccinimide in carbon tetrachloride. They hydrolyzed this group off with $CaCO_3$ in water.

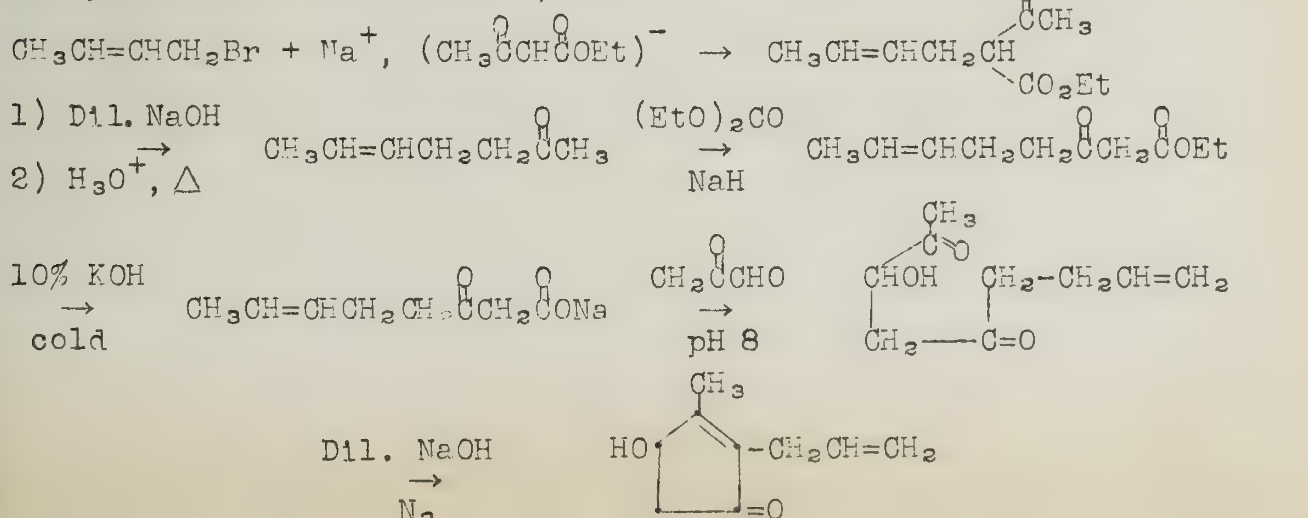
With eventual commercial preparation in mind, Campbell and Harper (12) set out to improve the method used earlier to prepare chrysanthemum monocarboxylic acid, which gave only a 15% yield. They used β-methallyl chloride as a starting material, employing a method recently reported for making 2,5-dimethyl-2,4-hexadiene (13).

$$CH_2{=}\underset{CH_3}{C}{-}CH_2Cl \xrightarrow[\text{dry ether}]{Mg} CH_2{=}\underset{CH_3}{C}CH_2CH_2\underset{CH_3}{C}{=}CH_2 \xrightarrow[\text{chromia-alumina}]{250^\circ} CH_3\underset{CH_3}{C}{=}CHCH{=}\underset{CH_3}{C}CH_3 \xrightarrow{N_2CH\overset{O}{C}OEt} 64\% \begin{cases}\text{DL-cis-acid}\\ \text{DL-trans-acid}\end{cases} + N_2$$

The DL-cis-acid is less soluble and higher melting than the DL-trans acid. The two acids may be readily separated.

Harper's group brominated synthetic compounds of type VI, where R was always saturated, by the method of Soloway and LaForge and reacted them with the silver salt of synthetic chrysanthemum monocarboxylic acid. The pyrethrins so made were of low activity (14).

The latest work in this field (15) is the total synthesis of some pyrethrins more active than the natural pyrethrins, by the group in this country. Since the method of bromination previously used to introduce the bromine atom, and subsequently the hydroxyl group, into position 4 of the ring was not applicable when the side chain was unsaturated, the most important thing in this article is the development of a ring synthesis in which the hydroxyl group was preformed. (See below.)

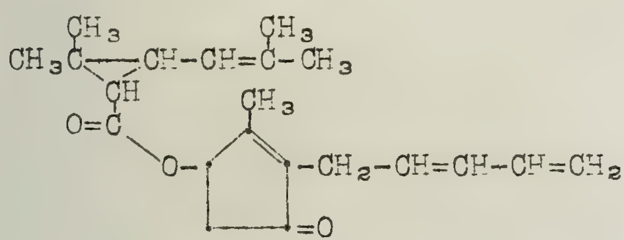


These preparations utilized commercially available starting materials. Although the yields are fair, they could undoubtedly be improved by further study and large scale reactions.

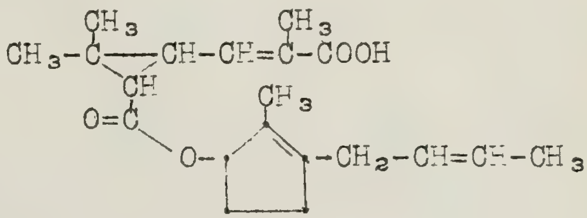
The authors esterified the alcohols in benzene solution with chrysanthemum monocarboxylic acid chloride using a pyridine catalyst.

The side chains on the alcohol fragment were quite varied, but most of the compounds exhibited a high order of insecticidal activity.

Thus a technical synthesis of pyrethrum type insecticides appears to have been brought within the realm of possibility.



Pyrethrin I



Cinerin II

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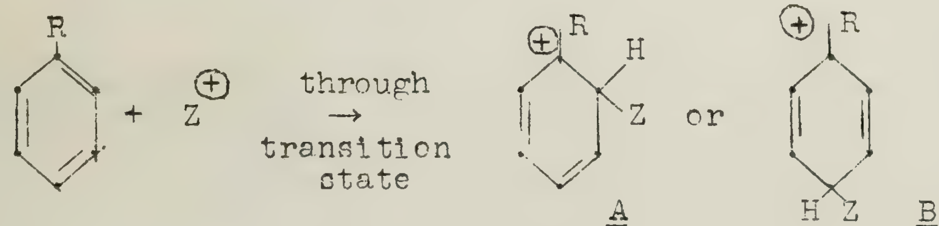
THE ORTHO: PARA RATIO IN AROMATIC SUBSTITUTION

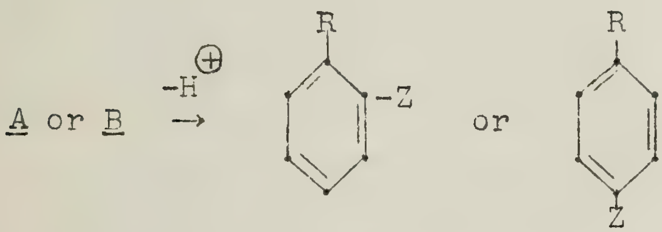
Reported by Roy H. Bible March 31, 1950

Although it has now been more than twenty years since the essential difference between ortho-para and meta types of benzene substitution was clearly explained by electronic considerations, the great variation in the ortho: para ratio has not yet received a fully satisfactory electronic interpretation (8). Various writers have recently dealt with several aspects of this problem, however, and the main features of the experimental data have been interpreted and summarized by de la Mare (1).

The generally accepted mechanism of aromatic substitution by electrophilic reagents can be represented by the following equations:

(1) $Y{:}Z \rightleftarrows Y{:}^{\ominus} + Z^{\oplus}$ or $Y^{\delta\ominus}\text{—}Z^{\delta\oplus}$

(2) 

(3) 

Recent work (2) has confirmed the actual existence of the transition state. Kinetic studies (3,4) made in the past few years indicate that in the halogenation processes the attacking species is not $X^{\oplus}$ but is probably the positive end of a dipolar halogen molecule.

By considering the experimental evidence, de la Mare has concluded that the following factors are of importance in determining the ortho: para ratio:

(I) For most ortho-para directing substitutents, the 1/2 ortho:para ratio is less than unity. (The 1/2 is introduced because there are two ortho positions and only one para.) There are two factors which contribute to this effect:

(a) Steric considerations favor para substitution. Small energy effects are revealed much more readily by chemical reactivities than by studies of isomerism or bond angles. The possible magnitude of the steric factors involved in aromatic substitution is indicated by the fact that in picryl iodide the three atoms of each of the two o-nitro groups lie in a plane

which is at an angle of 80° to the plane of the ring (5). De la Mare maintains that if the decrease in the 1/2 _ortho_: _para_ ratio for nitration along the series: $PhCH_3$, PhC_2H_5, $PhCH(CH_3)_2$, $PhC(CH_3)_3$ from 0.8 to 0 is interpreted primarily on the basis of the steric factor, then a large portion of the decrease of the 1/2 _ortho_: _para_ ratio for nitration along the series: $PhCH_3$, $PhCH_2Cl$, $PhCHCl_2$, $PhCCl_3$ from 0.8 to 0.1 must be due to steric hindrance.

(b) The greater stability of the _para_- than the _ortho_-quinoid structure favors _para_, since, as indicated in equation (2), the transition states for the reaction are analogous to such quinoid forms. The _para_-benzoquinones, in general, are more stable than the corresponding _ortho_-derivatives by about 4.5 kcal. (8).

(II) Substitution is favored _ortho_ to groups polarizable by induction, and occasionally this factor is sufficient to reverse the order expected on steric grounds.

The prediction of the 1/2 _ortho_: _para_ ratio for nitration of the halobenzenes on the basis of steric hindrance alone would give the series: PhF > PhCl > PhBr > PhI which is the reverse of the observed order. Prediction of the ratios only on the basis of the electronegativities gives the correct order, but this appears to be an over simplification since the overall rate of nitration for the series is in the order: PhF > PhI > PhCl > PhBr rather than in the order: PhI > PhBr > PhCl > PhF. De la Mare and Robertson (3) have interpreted the facts as being the result of a polarizability effect the order of which is I > Br > Cl > F.

(III) For many _meta_ directing groups in which a resonance deactivation of the aromatic ring is important, the 1/2 _ortho_: _para_ ratio is much above unity. For example, for nitration the results given in table I are found.

Table I - The 1/2 _Ortho_:Para Ratio for Nitration at 0°C (7)

X in PhX	1/2 (o/p)
$-CO_2C_2H_5$	4.3
$-COOH$	7.1
$-NO_2$	12.8

Here again the quinoid structures may be more important in transferring the charge to the _para_ than to the _ortho_ position. Since the transferred charge is a positive one, the _para_ position is deactivated relatively to the _ortho_ position by electrostatic replusion of the reagent (or otherwise).

(IV) For some compounds _ortho_ substitution depends to a great extent on the reagent. Three generalizations can be made here:

(a) Substitution _ortho_ to a polarizable group should be favored by an ionic, as compared with a neutral or dipolar reagent. It has been suggested that this factor accounts for the differences

between the effects of halogen substituents on the nitration and halogenation of aromatic compounds. This difference can be seen in table II. It is reasoned that the nitronium ion evokes the polarizability more than the dipolar halogen molecule.

Table II - Effect of Halogen Substituents on the 1/2 Ortho:Para Ratio for Nitration and Halogenation (7)

	NO_2-	Br-	Cl-
PhCl	0.218	0.0643	0.355
PhBr	0.301	0.0770	0.395

(b) Ortho substitution should be favored by a small as compared with a large reagent. The influence of the size of the reagent has often been pointed out to account for such facts as the decrease of the 1/2 ortho: para ratio for toluene from 0.69 to 0.26 in going from nitration to sulfonation (7).

(c) Ortho substitution should be favored by chelation in the transition state between the reagent and the ortho substituent (8). This point was brought out in a recent seminar (9). Chlorination and nitration of phenol, for example, give comparable amounts of ortho- and para-products but bromination yields the para-compound almost exclusively as is shown in table III.

Table III - Introduction of a Second Substituent into Phenol (7)

	1/2 (o/p)
Cl	0.495
NO_2	0.333
Br	0.0545

It is known that hydrogen bonding is important in o-chlorophenol and in o-nitrophenol but is not important in o-bromophenol (8).

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ISOMERIZATION OF $\alpha\beta$-UNSATURATED ACIDS

Reported by R. L. Foster March 31, 1950

One of the first instances of $\alpha\beta$-$\beta\gamma$ isomerism was reported in 1894 by Fittig (1). The acids which he investigated (I and II) were obtained as perfectly stable isomers. The acids were, however, interconvertible in alkaline solution, with the equilibrium predominately on the $\alpha\beta$ side. The migration of the double

$$CH_3CH{=}CHCH_2CO_2H \rightleftharpoons CH_3CH_2CH{=}CHCO_2H$$

I II

bond into conjugation with the carbonyl, because of the predominance of the α,β form in the equilibrium mixture, was so general that it became known as Fittig's rule.

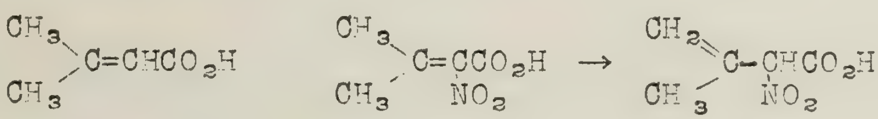
An exception to the rule was found in cyclohexylidene-acetic acid (III n=2), which is converted almost completely to cyclohexene-1-acetic acid (IV n=2)(2). Similarly cyclopentylidene-acetic acid (III n=1) is converted to cyclopentene-1-acetic acid. (IV n=1) (3).

III IV

Further examples of this type of isomerism are $\beta\beta$-diethylacrylic acid (V R=CH_3) and β-ethyl β-methylacrylic acid (V R=H), which are converted largely to β-ethylidene valeric acid (VI R=CH_3) and β-ethylidene butyric acid (VI R=H) when heated with alkali.

V VI

$\beta\beta$-Dimethylacrylic acid (VII) does not isomerize under any conditions which were tried (3), and vinylacetic acid rearranges completely to crotonic acid. (4)

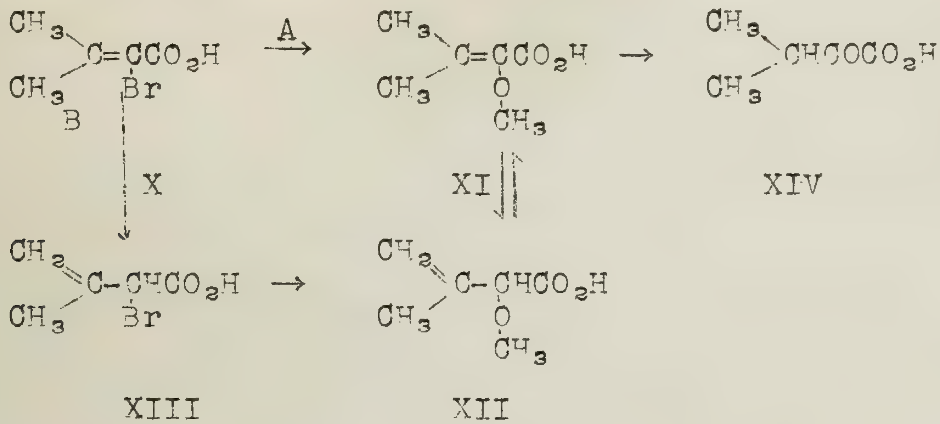


VII VIII IX

The only report of isomerization of derivatives of VII was that of α nitro $\beta\beta$-dimethylacrylic acid (VIII), which on treatment with alkali gives αnitro βmethylene butyric acid (IX). (5)

Recently Owen and Sultanbawa have shown that a rearrangement of α-bromo ββ-dimethylacrylic acid must occur during reaction with alkoxides. (6,8)

In the reaction of α-bromo ββ-dimethylacrylic acid (X) with sodium methoxide, a mixture of α methoxy ββ-dimethylacrylic acid (XI and α-methoxy β-methylene butyric acid (XII) was formed. (6) The βγ-unsaturated isomer was not expected since there was no such rearrangement in the crotonic acid series. (7)



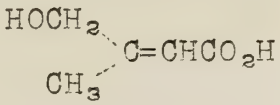
A solid isomer (XI) and a liquid isomer (XII) were obtained in the reaction. The position of the double bond in XI was established by U.V. absorption, showing a conjugated double bond, and by hydrolysis of the enol ether to α keto isovaleric acid (XIV). The other isomer (XII) showed no conjugation and on ozonolysis gave formaldehyde. Similar results were obtained when sodium ethoxide was used. (6)

A mixture of the two isomers could be obtained either by path A or B. If the reaction proceeded by A, the proportion of the βγ isomer XII should increase as the reaction continues; if reaction B occurs the proportion of XI should increase. In a six hour reaction period mainly the βγ unsaturated isomer was obtained. When the reaction was continued for 24 hours the αβ isomer was the main product. The reaction must then follow B, with formation of XIII as an intermediate. (8)

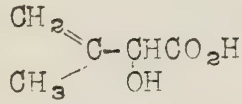
Beginning with either isomer (XI or XII) an equilibrium mixture containing over 90% of the αβ unsaturated isomer was obtained by heating with alkali.

In replacing the bromine of α-bromo β-methylene butyric acid (XIII) there might be either direct replacement or rearrangement to give a γ-alkoxy αβ unsaturated acid. It is known, however, that rearrangement occurs only when S_n1 mechanism is possible, and not under the bimolecular conditions which were employed. (9) When α-bromo ββ-dimethylacrylic acid was treated with aqueous alkali, rearrangement did occur and three products were identified; α keto isovaleric acid (XIV), γ-hydroxy β-methylcrotonic acid (XV),

and α hydroxy β methylene butyric acid (XVI). α Hydroxy



XV



XVI

β methylene butyric acid (XVI) on heating with alkali gave α keto isovaleric acid (XIV) by rearrangement of the double bond and ketonization. (8)

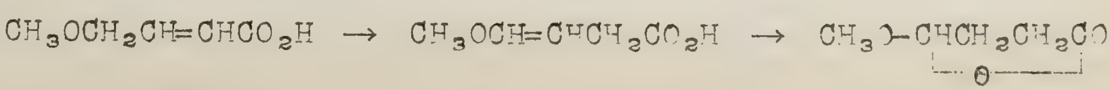
It is interesting to compare the reaction of alkoxides with α bromoacrylic, α bromo-crotonic, and α bromo ββ-dimethylacrylic acids. With α bromo acrylic acid the main reaction is that of addition to the double bond followed by elimination of HBr. αβ Dialkoxy propionic acid is also formed either by addition of a second alkoxy group or replacement of bromine in the intermediate α bromo β methoxy propionic acid.

α Bromo crotonic acid reacts with alkoxides to give α alkoxy crotonic acid and also a small amount of β alkoxy crotonic acid. The β alkoxy compound is formed by addition to the double bond and elimination of HBr. The α alkoxy derivative is obtained by isomerization of α bromo crotonic acid to the βγ-unsaturated isomer, the bromine is then replaced directly by the alkoxy group, and the double bond then shifts back to the αβ position. The fact that no βγ unsaturated isomer has been obtained is explained by the rapid attainment of equilibrium which is almost entirely on the αβ side. In α bromoacrylic acid there is no βγ position to which the double bond could move, and there is no α alkoxy acrylic acid obtained.

In α bromo ββ-dimethylacrylic acid the extra methyl group on the β carbon tends to prevent addition to the double bond, so substitution is the reaction observed. The rate of attainment of equilibrium in this case is slower and both the αβ and βγ-unsaturated α alkoxy acids were obtained. (7, 8)

In other compounds where there is no opportunity for a shift of the double bond, no substitution of the α bromine has been observed. Thus $C_6H_5CH{=}CBrCO_2H$ and $HO_2CCH{=}CBrCO_2H$ give only elimination of HBr when heated with alkali. (8)

In order to determine the effect of an alkoxy group in the γ position, γ methoxy-crotonic acid (XVII) was prepared. On heating with aqueous alkali this acid is converted into 4-methoxy-3-butenoic acid (XVIII). The equilibrium mixture of XVII and XVIII contains about 70% of the βγ unsaturated isomer. The βγ-unsaturated isomer showed lactonic properties and probably exists partly as the lactone (XIX). (10).



XVII XVIII XIX

The equilibrium mixtures given by β and γ methoxy-crotonic acids by treatment with alkali contain about 60% and 70%, respectively, of the βγ isomer. No βγ isomer was detected on similar treatment of α methoxy crotonic acid. Attempts to prepare other γ methoxy αβ-unsaturated acids were unsuccessful. (10)

The reaction of α bromo γ methoxy crotonic acid with alkali leads to a mixture of products. Products corresponding to addition, substitution, and rearrangement were obtained along with polymeric material. A free carbonium ion appears to be formed in the reaction. (11)

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THE "VINYL INTERCHANGE" REACTION

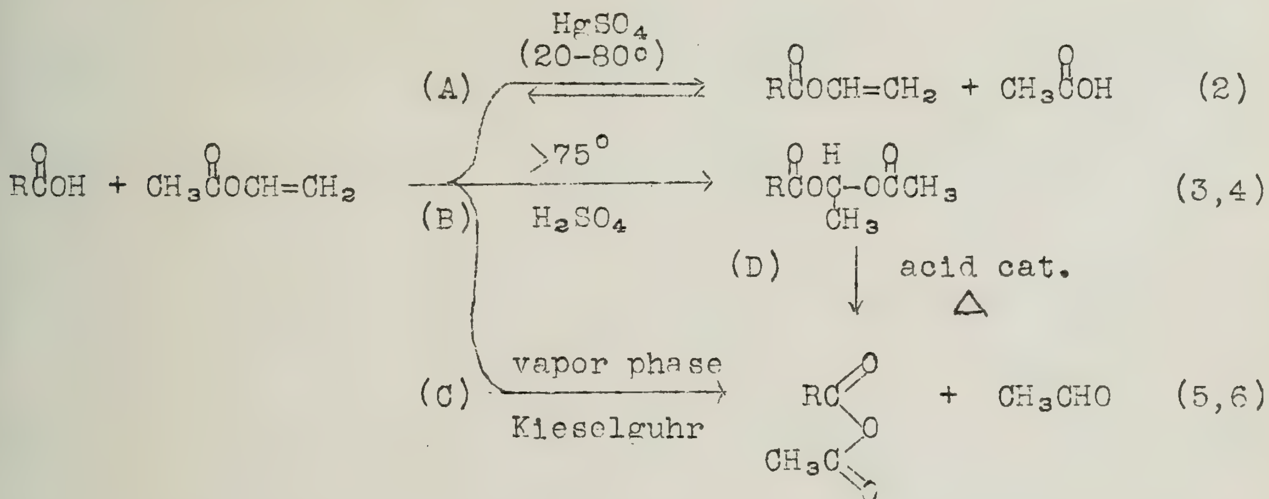
Reported by S. Mark Cohen April 14, 1950

The reaction of vinyl acetate with carboxylic acids, in the presence of mercuric salts of strong acids, has been found to produce the vinyl ester of the acid (1,2,11).

$$RCOOH + CH_3\overset{O}{\overset{\|}{C}}OCH{=}CH_2 \xrightarrow{HgSO_4} RCOOCH{=}CH_2 + CH_3COOH$$

This reaction is called the "Vinyl Interchange" reaction to differentiate it from the typical ester interchange and ester-acid interchange reactions. Because of its very mild reaction conditions, low yields of by-products and high yields of monomer, this is a useful method for the laboratory preparation of many of the simpler vinyl esters, superior to the reaction of acetylene with acids (11).

There are three possible major reactions of vinyl acetate with carboxylic acids, depending upon the temperature of reaction and the catalyst (Equations A, B, C).



Reaction (A), the vinyl interchange reaction, produces very high yields of vinyl esters if the reaction temperature is kept at 30° or below. However, since the reaction is reversible, a period of days may be required before the interchange achieves a final equilibrium value (11).

It is believed that the mechanism involved here proceeds through the dissociation of the vinyl acetate, in the presence of mercuric sulfate catalyst, into an acetylene-mercury complex, which is then capable of reacting further with the various acids present to form the vinyl derivatives (Equations I, II).

$$\text{(I)}\quad CH_3\overset{O}{\overset{\|}{C}}OCH{=}CH_2 + HgSO_4 \rightleftarrows CH_3\overset{O}{\overset{\|}{C}}OH + \underset{HgSO_4}{HC{=}CH}$$

$$\text{(II)}\quad \mathrm{R\overset{O}{\overset{\|}{C}}OH + \underset{\diagdown HgSO_4 \diagup}{HC{=}CH}} \rightleftarrows \mathrm{R\overset{O}{\overset{\|}{C}}OCH{=}CH_2 + HgSO_4}$$

If this is so, the reaction must proceed with a breaking of the oxygen-hydrogen bond in the acid and the oxygen-vinyl carbon bond in the vinyl ester, as shown in equation III.

$$\text{(III)}\quad \mathrm{R\overset{O}{\overset{\|}{C}}{-}O\vdots H + CH_3\overset{O}{\overset{\|}{C}}{-}O\vdots CH{=}CH_2} \rightarrow \mathrm{R\overset{O}{\overset{\|}{C}}OCH{=}CH_2 + CH_3\overset{O}{\overset{\|}{C}}OH}$$

This is quite different from the mechanism of typical ester-acid interchanges, where the carbonyl carbon-to-oxygen bond is broken in the ester and the carbon-oxygen bond is broken in the acid, as in equation IV (7,11).

$$\text{(IV)}\quad \mathrm{R\overset{O}{\overset{\|}{C}}\vdots OH + CH_3\overset{O}{\overset{\|}{C}}\vdots O{-}C_2H_5} \rightarrow \mathrm{R\overset{O}{\overset{\|}{C}}O{-}C_2H_5 + CH_3\overset{O}{\overset{\|}{C}}OH}$$

Support for this mechanism is found in the following evidence:

(a) There are marked differences in vinyl interchange reactions as compared to ester interchanges or acid-ester interchanges. For example, ester-acid or ester-ester interchanges are catalyzed by acids or bases (although different mechanisms are postulated for the two cases) (7), whereas the vinyl interchange is not catalyzed by either acids or bases (11). Furthermore, the well-known interchange between two different carboxylic acid esters, such as

$$\mathrm{RCOOR' + R''COOR'''} \underset{\text{or } (OH^-)}{\overset{(H^+)}{\rightleftarrows}} \mathrm{RCOOR''' + R''COOR'}$$

has not been successfully carried out when one of the esters is a vinyl ester. Also, those acids which normally would undergo acid-catalyzed esterifications or ester interchanges much more slowly than straight chain acids because of steric hindrance, such as trimethylacetic acid and <u>ortho</u>-substituted benzoic acids, have no difficulty in undergoing the vinyl interchange because the actual locus of reaction occurs farther away from the interfering groups, being more distant by one oxygen atom (8,11).

(b) A possible mechanism involving the ethylidene diester as an intermediate followed by decomposition to the vinyl ester is unacceptable, since the vinyl ester interchange reaction is not catalyzed by acids, whereas the formation of ethylidene diesters is subject to general acid catalysis.

$$\mathrm{RCOOH + CH_3\overset{O}{\overset{\|}{C}}OCH{=}CH_2} \rightarrow \left[\mathrm{CH_3\overset{O}{\overset{\|}{C}}O\underset{CH_3}{\overset{H}{C}}O\overset{O}{\overset{\|}{C}}R}\right] \not\rightarrow \mathrm{CH_3COOH + R\overset{O}{\overset{\|}{C}}OCH{=}CH_2}$$

Moreover, it is estimated that the formation of ethylidene diesters requires a greater energy of activation than the formation of vinyl esters and so could not act as an intermediate at room temperature. The heat of activation can be estimated qualitatively by the fact that the amounts of ethylidene diesters increased as the reaction temperature was raised (9,11).

(c) Acetylene plus various active hydrogen compounds produce identical products, under similar conditions, as vinyl acetate with the same active hydrogen compounds. Acids and bases are not catalysts for the vinyl interchange reaction nor also for the reaction of carboxylic acids with acetylene at low temperatures. Both reactions postulate an acetylene catalyst complex as an intermediate (10). Further similarity between the reactions of acetylene and vinyl acetate was found when both yielded the same product in reaction with a labile H of the type R-H (11).

$$CH_3\overset{O}{\overset{\|}{C}}CH_2COOC_2H_5 + CH_3COOCH{=}CH_2 \xrightarrow[75^\circ]{HgSO_4} CH_3\overset{O}{\overset{\|}{C}}\overset{CHCH_3}{\overset{\|}{C}}OOC_2H_5 + CH_3COOH$$

$$2(HOCH_2COOCH_3) + CH_3\overset{O}{\overset{\|}{C}}OCH{=}CH_2 \xrightarrow[75^\circ]{HgSO_4} CH_3\overset{H}{C}{=}(OCH_2COOCH_3)_2 + CH_3COOH$$

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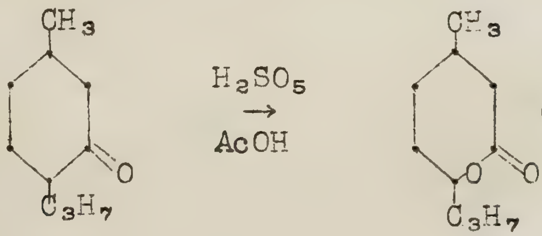
NON-FREE RADICAL REACTIONS OF PERACIDS WITH CARBONYL COMPOUNDS

Reported by John Figueras April 14, 1950

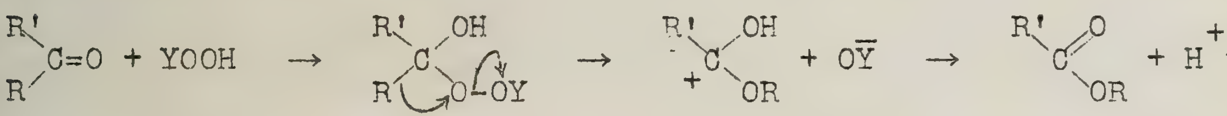
In 1899, Baeyer and Villiger (1) found that Caro's acid (H_2SO_5) reacted with terpenones as follows:



ca. 85% yield

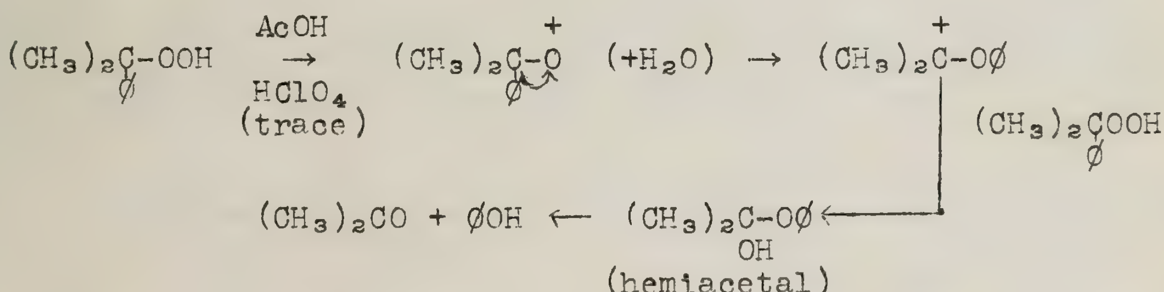
Other cyclic ketones will react analogously. Organic peracids have been found to be useful reagents for bringing about this reaction (2,3). The preparation and uses of peracids have been covered in a review article by Swern (4).

The mechanism for peroxidations with Caro's acid has been reviewed in a previous seminar (5,6). Karrer (7) has generalized this mechanism to include the organic peracids:

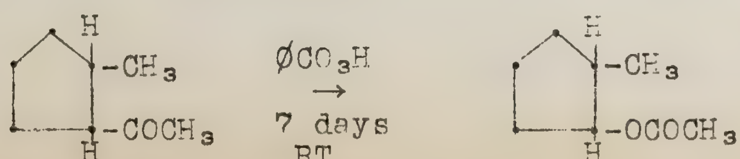


Y = SO_3H, ØCO, CH_3CO, H, or phthaloyl

Criegee (8) has postulated a similar mechanism for the rearrangement of decalin hydroperoxide benzoate (see also (9)). Kharasch (10) noted a rearrangement of hydroperoxides in the presence of strong acid, the mechanism of which resembles that just given:

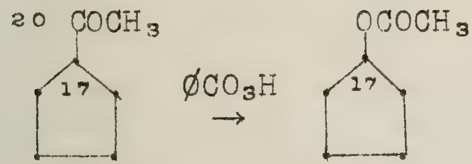


Kharasch found, from a series of such reactions, that the most electron-releasing group migrated - a fact mentioned by Robertson and Waters (6) in connection with the reaction of Caro's acid with ketones. Turner (11) has shown that the peroxidation of ketones proceeds with retention of configuration of the migrating group:



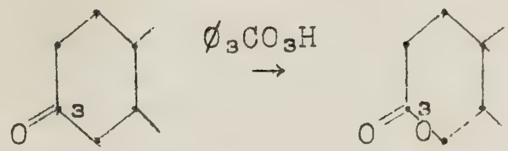
<u>cis</u> → <u>cis</u> (66% yield) } as 3,5-dinitro-
<u>trans</u> → <u>trans</u> (64% yield) } benzoates

The same results, and equally good yields, were obtained with <u>cis</u>- and <u>trans</u>-1-acetyl-2-methylcyclohexanes. These results were confirmed by Gallaher and Kritchevsky (12), who found that 20-keto steroids underwent peroxidation with retention of configuration at C-17 (fig. I).



C17-α → C17-α
C17-β → C17-β

I



II

Sarett (13) obtained excellent yields of the C-17 acetates from 20-keto steroids; he reports that the reaction proceeds with <u>inversion</u> at C-17. Marker and coworkers (14,15) have carried out analogous peroxidations with Caro's acid, and obtained 30-35% yields of the corresponding acetates. 3-keto steroids are oxidized to the corresponding lactones (fig. II) in yields of 30-60% by perbenzoic acid (16).

Aliphatic aldehydes, because they are so easily oxidized, do not undergo the expected rearrangement with peracids in good yield (17):

$$\mathrm{RCHO} \xrightarrow[\text{ether}]{H_2O_2} \mathrm{RCOOH} + [\mathrm{RO{-}CHO}] \rightarrow \underset{\text{ca.}50\%}{\mathrm{RCOOH}} + \underset{3\text{-}9\%}{\mathrm{ROH}} + \mathrm{HCOOH}$$

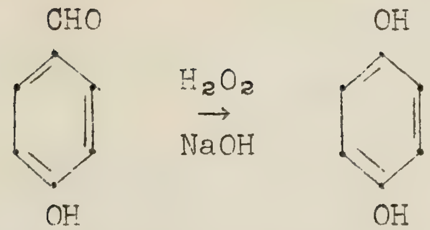
Swern (4) noted that aliphatic aldehydes are oxidized to the corresponding acids in excellent yield by peracids. An exception to this is citral (18), which goes to an epoxy aldehyde of one carbon atom less. The following reaction course was postulated by Karrer (7):

$$(CH_3)_2C{=}CHCH_2CH_2\underset{CH_3}{C}{=}CHCHO \xrightarrow{\phi CO_3H} (CH_3)_2C\overset{O}{\text{—}}CHCH_2CH_2\underset{CH_3}{C}{=}CH{-}O{-}CHO$$

$$\downarrow H_2O$$

$$(CH_3)_2C\overset{O}{\text{—}}CHCH_2CH_2\underset{CH_3}{C}HCHO \leftarrow (CH_3)_2C\overset{O}{\text{—}}CHCH_2CH_2\underset{CH_3}{C}{=}CH{-}OH$$

Aromatic <u>o</u>- and <u>p</u>-hydroxy aldehydes and ketones are presumably peroxidized in accord with the above mechanism (7) - this constitutes the Dakin reaction (19):



The Dakin reaction employs alkaline hydrogen peroxide. A similar reaction has been effected using peracetic acid with piperonal and related compounds (20).

α,β-unsaturated ketones react with peracids in a manner analogous to that of the saturated ketones (20,21,22). Alkaline hydrogen peroxide, however, gives epoxy compounds (23):

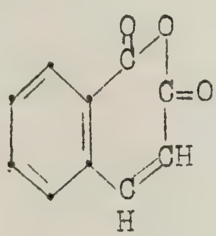
$$\text{Ø-CH}\overset{\text{O}}{\frown}\text{CHCOCH}_3 \xleftarrow[\text{NaOH}]{H_2O_2} \text{ØCH=CHCOCH}_3 \xrightarrow{CH_3CO_3H} \text{ØCH=CH-O-COCH}_3$$

Karrer and coworkers have investigated the peroxidations of 1,2-diketones. The net result of these reactions is the insertion of an oxygen atom between the two carbonyl groups to give anhydrides:

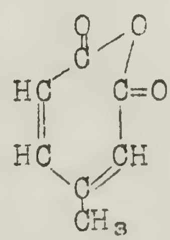
$$(24,25)\,[\text{Ø(CH=CH)}_2\text{CO}]_2 \xrightarrow[\text{acid}]{\text{perphthalic}} [\text{Ø(CH=CH)}_2\text{CO}]_2\text{O} \xrightarrow[H_2SO_4]{\text{alc.}} \text{Ø(CH=CH)}_2\text{COOH}\ \ 60\text{-}75\%\text{yield}$$

$$(26)\ CH_3COCOCH_3 \xrightarrow[\text{acid}]{\text{perphthalic}} [(CH_3CO)_2O] \xrightarrow{NH_3} CH_3CONH_2 + CH_3COONH_4$$

Dipropionyl gave similar results (26). The anhydrides formed in these reactions were not isolated as such, but characterized as derivatives. Ortho-quinones behave analogously. 1,2-Naphthoquinone treated with perbenzoic acid in chloroform gives o-carboxy-allo-cinnamic acid anhydride (fig. III) and 4-methyl-o-benzoquinone gives cis-cis-β-methylmuconic acid anhydride (fig. IV) on treatment with perphthalic acid (27,28):



III



IV

α-Keto esters behave as might be expected on the basis of these examples (8):

$$CH_3COCOOC_2H_5 \xrightarrow[\text{acid}]{\text{perphthalic}} CH_3CO\text{-}O\text{-}COOC_2H_5$$

$$\text{Ø}COCOOC_2H_5 \xrightarrow{\text{"}} \text{Ø}CO\text{-}O\text{-}COOC_2H_5$$

The products are mixed anhydrides of organic acids and the halfester of carbonic acid. These reactions proceed in poor yield due to the difficulty in isolating the final product.

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REDUCTIONS BY SODIUM IN LIQUID AMMONIA AND ALCOHOL

Reported by Thomas G. Miller April 14, 1950

Reductions by solvent-dissolving metal combinations have been replaced in many cases by more convenient catalytic methods. In certain cases, however, the specific reactivity of these combinations makes their use advantageous. With this idea in mind, Birch has investigated sodium, in combination with a liquid ammonia-alcohol mixture, as a reducing agent for reactions in which catalytic methods are not particularly successful. In general, this combination will reduce: (a) acetylenes to ~~cis~~ trans olefins, (b) unsatured functional groups, and (c) conjugated systems, either aliphatic, aromatic, or mixed (1). Hydrogenolysis of benzyl and allyl type alcohols can also be accomplished (2). Isolated olefinic double bonds are not affected. Common side reactions encountered are: (a) isomerization of double bonds, (b) cleavage of alkyl-aryl ethers, and (c) loss of alkoxyl groups from dialkoxybenzenes (3,4).

The mechanism of Na-NH_3-alcohol reduction is not well established. Many of the reactions indicate that it is ionic, with the first step involving the addition of electrons to the conjugated system. A proton donor is needed in the reaction mixture, however, for the results are generally poor when Na and NH_3 are used alone (5).

The net result of the reduction of aromatic rings is the 1,4 addition of hydrogen. Since the conjugated system is destroyed in the process, the reaction stops after one step unless isomerization of the remaining double bonds occurs. Vigorous conditions are needed in order to bring about the reduction of aromatic nuclei.

Alkylbenzenes Reduced

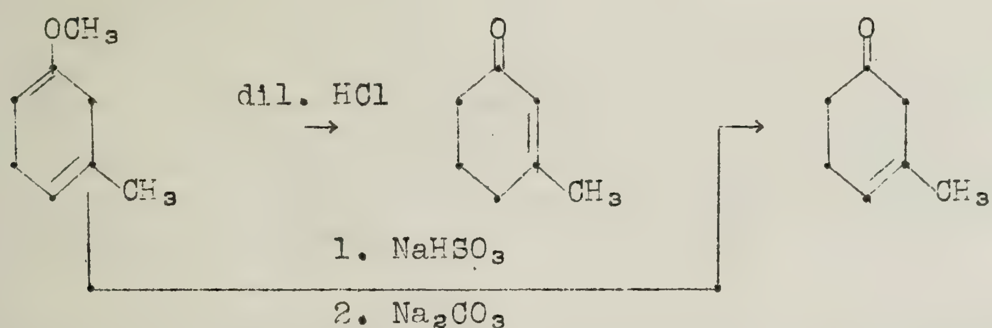
Compound	Addition	Yield	Ref.
tetralin	5-8	not given	5
m-xylene	2-5	" "	5
p-xylene	2-5	" "	5
1,4-$CH_3C_6H_4CH(CH_3)_2$	2-5	" "	5
toluene	2-5	" "	4
α-curcumene	2-5	91%	1

Because of the small differences in boiling points of the starting material and the product, there is some difficulty in separating the mixture, extensive fractionation being necessary in most cases. In general, hydrogen is added to unoccupied places on the ring (5).

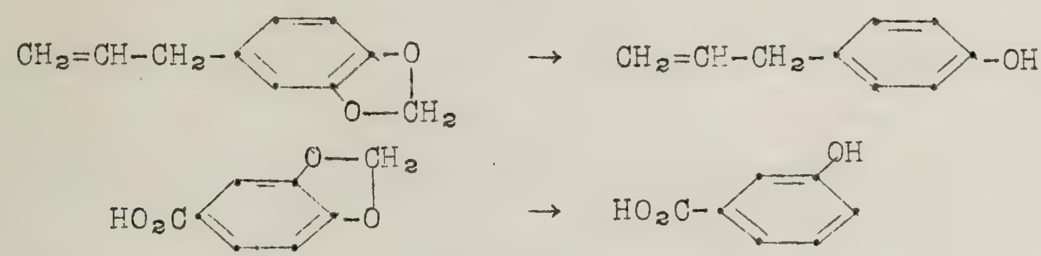
All isomers of methyl- and dimethyl-anisole were reduced to the corresponding dihydro derivatives by this method (5,6). Yields of ca. 70% were obtained when the hydrogen donor was kept in excess throughout the reaction (6). With these compounds also the

orientation of the added hydrogen was away from electron donating groups or positions para to such groups. In those cases in which such a position could not be avoided, e.g. 3,5-dimethylanisole, the yields were lowered. A methoxyl group exerts a stronger orientating effect than a methyl group.

The dihydroanisoles formed by this method are easily hydrolyzed to the corresponding α-β, or β-γ unsaturated ketones, the former by simultaneous ether cleavage and isomerization with dilute mineral acids, the latter by cleavage with sodium bisulfite followed by treatment with sodium carbonate (6).



Resorcinol and hydroquinone dimethyl ethers are reduced in 90% yield to dihydro derivatives. Under the same conditions, however, catechol dimethyl ether loses a methoxyl group, the final product being 2,5-dihydroanisole (3). Methylenedioxybenzenes undergo a similar cleavage along with loss of a hydroxymethylene group. Methylenedioxybenzene itself is converted in 77% yield to phenol. The nature of substituents in the para position determines the point of cleavage of these compounds, oxygen being lost at the point of lowest electron density, i.e. meta to a para directing group and para to a meta directing group (3,7).



In a similar cleavage using Raney nickel in basic solution, Papa and Schwenk observed that para cleavage occurred regardless of the nature of the substituent (8).

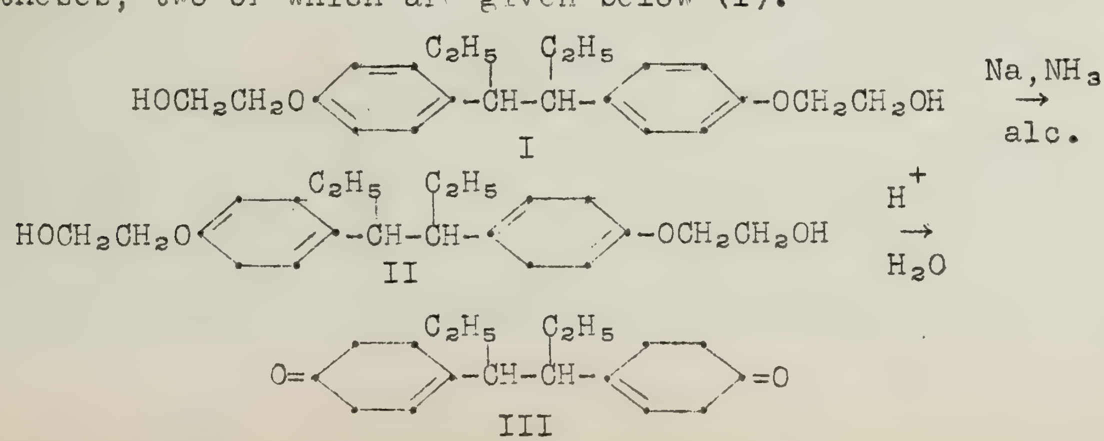
A number of naphthalene derivatives were also reduced with sodium in ammonia and alcohol, α-naphthol giving 5,8-dihydro-α-naphthol (85%), and β-naphthol giving β-tetralone (65%). 6-Methoxytetraline gave 44% of the 5,8-dihydro compound isolated as the corresponding ketone, and 5-methoxyhydrindene was hydrogenated in the 4-7 positions (5). 1-Naphthoic acid was reduced in the 1-4 positions.

Dimethylanilines, toluidines, and xylidines may be reduced to dihydro derivatives in yields comparable to those of the anisoles (6). The rules of orientation given previously apply in this case also. Hydrolysis of the primary reduction product from o- and M- toluidines gives the corresponding α-β unsaturated ketone. Isomerization of the double bond does not occur with the p- derivatives, however, and the product is a β-γ unsaturated ketone.

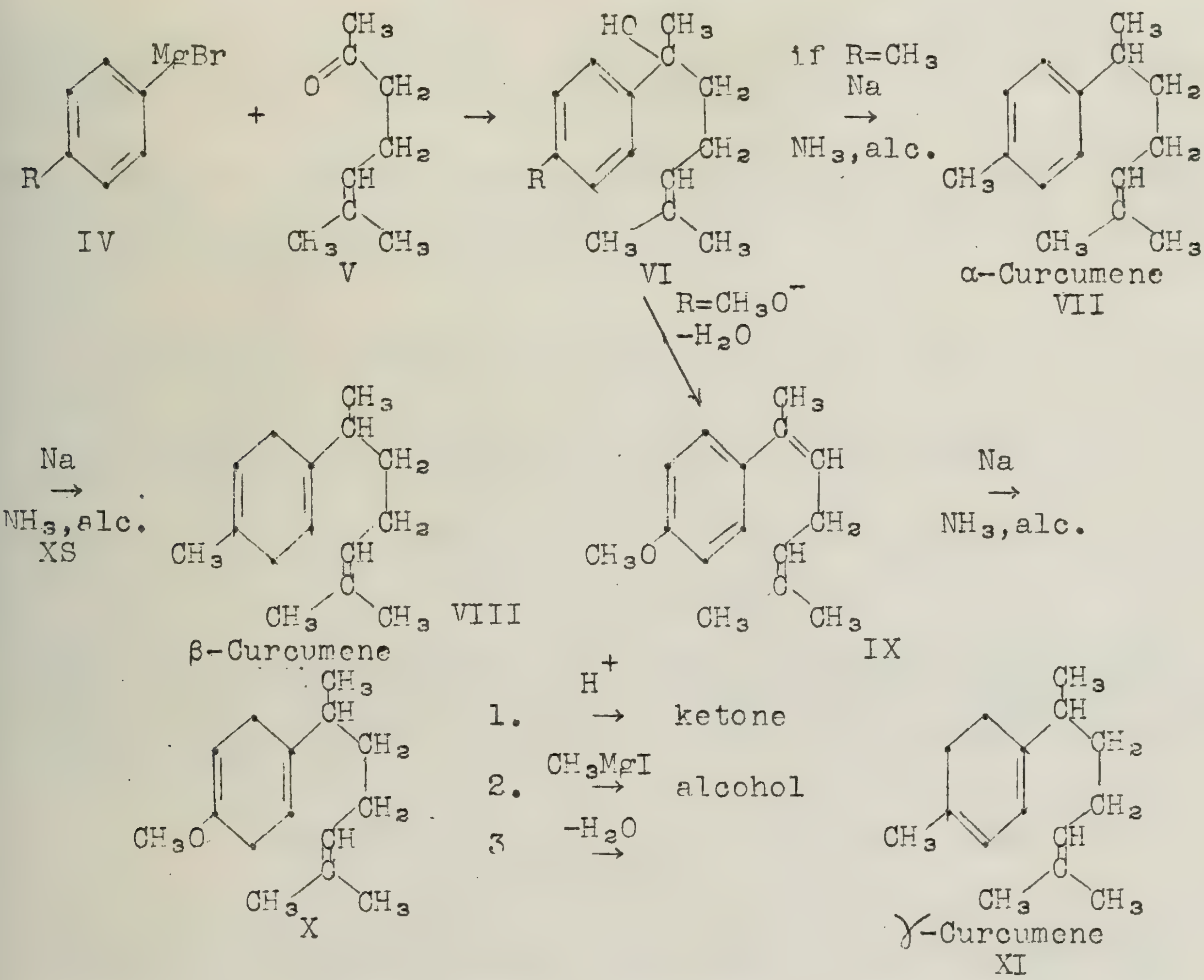
Hydrogenolysis of allyl and benzyl alcohols may be accomplished using sodium in ammonia and alcohol (2). As a synthetic method this reaction is advantageous in that isolated olefin bonds are not attacked, and due to the milder conditions employed aromatic rings are also untouched. Isomerization of allyl alcohols may occur, however. Benzyl alcohol, phenylmethylcarbinol, phenyldimethylcarbinol, and phenylbutylcarbinol are reduced almost quantitatively to the corresponding hydrocarbons. A methoxyl group in the para position reduces the yields to ca. 20%. Furfurylcarbinols are also resistant to hydrogenolysis. In general, the ease of hydrogenolysis corresponds roughly to the stability of the carbanion intermediate.

Isomerization of dihydrobenzenes to conjugated dienes with KNH_2 and further reduction with $Na-NH_3$-alcohol was investigated. In all cases inseparable mixtures were obtained (4).

As a synthetic tool, reduction by $Na-NH_3$-alcohol has several advantages and several disadvantages. Its power and specificity are useful, and the solvent is easily removed. Its usefulness is lessened by the low solubility of some compounds, chiefly higher hydrocarbons, in the solvent. Large amounts of material are also difficult to work with. Birch has used the reduction in a number of syntheses, two of which are given below (1).



In the synthesis above hydroxyethyl ethers are employed in order to increase the solubility of the starting material in ammonia. This also affords better separation by distillation, since the hydroxyethyl ethers of the unchanged starting material are not hydrolyzed by dilute acids, thus affording a greater difference in boiling points of the starting material and product.



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THE ACTION OF RANEY NICKEL ON ORGANIC SULFUR COMPOUNDS

Reported by Cal Y. Meyers April 21, 1950

Raney nickel reacts with organic sulfur compounds to give various products, depending on the mode of preparation of the catalyst and operating conditions.

The hydrogen in R-Ni is held by (4): a) Ni hydride combination, b) solution in the Ni, or c) adsorption on the Ni surface or as a combination of these. In any case, the hydrogen is free to react under very mild conditions.

I. Action of R-Ni as usually prepared (1,2,3): French workers (4,5) have found that mercaptans in neutral or alkaline solution and R-Ni generate nickel sulfide and sulfur-free organic compounds; a nickel mercaptide is an intermediate:

$$\text{RSH} \xrightarrow[\text{PH} \geq 7]{\text{Ni}} \text{RSNiSR} \rightarrow Ni_2S \text{ (+R-R and R-H)}$$

Mozingo et al. (6) have postulated that organic sulfur compounds react with R-Ni in two ways:

$$\text{RSR'} \xrightarrow{\text{Ni}} \begin{cases} \xrightarrow{a} \text{R-R' and R-R and R'-R'} \\ \xrightarrow{b} \text{R-H and R'-H} \end{cases}$$

Path "a" is a side reaction, "b" usually being followed if sufficient R-Ni (i.e., excess hydrogen) is present. Since "a" is called a "Wurtz-type" reaction, "b" also may be considered a free radical type (7):

$$(C_6H_5CH_2)_2S \xrightarrow[\text{boiling EtOH}]{\text{Ni}} 2C_6H_5CH_3 \quad 85\%$$

Under these mild conditions aromaticity is not destroyed. Sulfoxides and sulfones likewise give similar-type hydrocarbons:

$$C_6H_5SOC_6H_5 \xrightarrow[\text{"}]{\text{"}} 2C_6H_6 \quad 75\%$$

$$C_6H_5SO_2C_6H_5 \xrightarrow[\text{"}]{\text{"}} 2C_6H_6 \quad 65\%$$

The postulation that "a" is possible was proved by other workers (8).

II. Action of dehydrogenated R-Ni (8): Hauptmann (8,9,13) has found that a dehydrogenated R-Ni gives rise to various products depending upon the amount of dehydrogenation of the nickel.

A. $\text{R-Ni (1)} \xrightarrow[\text{in vacuo}]{200°}$ "Hydrogen-free R-Ni"

B. $\text{R-Ni} \xrightarrow{100°}$ "Hydrogen-poor R-Ni"

In the following, the sulfur compounds were refluxed in a suspension of the designated type of R-Ni in xylene. Wherever possible, the products were characterized by their crystalline sulfones.

Aromatic mercaptals, mercaptols, and disulfides in the presence of "A" give sulfides (8,9):

$$H_2C(SC_6H_5)_2 \xrightarrow{\text{"A"}} C_6H_5SC_6H_5 \qquad 71\%$$

$$C_6H_5SSC_6H_5 \xrightarrow{\text{"A"}} C_6H_5SC_6H_5 \qquad 82\%$$

But aromatic-aldehyde mercaptals and aromatic-ketone mercaptols give stilbenes in addition to sulfides:

$$C_6H_5CH(SC_6H_5)_2 \xrightarrow{\text{"A"}} (C_6H_5)_2S \;\; 88\% + C_6H_5CH{=}CHC_6H_5 \quad 60\%$$

$$C_6H_5\text{-}C(CH_3)\begin{matrix}\diagup S\text{---}CH_2 \\ \diagdown S\text{---}CH_2\end{matrix} \xrightarrow{\text{"A"}} C_6H_5C(CH_3){=}C(CH_3)C_6H_5 \quad 30\% \text{ \underline{Trans}-}$$

no sulfide isolated

The last example illustrates the general rule that sulfides are formed only if the sulfur is bound to an aromatic group:

$$C_6H_5CH(SCH_2C_6H_5)_2 \xrightarrow{\text{"A"}} C_6H_5CH{=}CHC_6H_5 + (C_6H_5CH_2)_2$$

All the sulfur in this type of reaction is bound on the nickel.

In the presence of "B" binuclear hydrocarbons are formed:

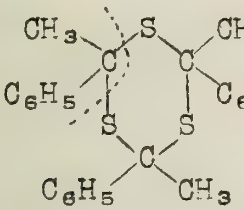
$$H_2C(SC_6H_5)_2 \xrightarrow{\text{"B"}} C_6H_5\text{-}C_6H_5 \quad 9.2\%$$

This is the side reaction, "a", postulated by Mozingo (see above). It was found that as the amount of hydrogen is increased, the yield of biphenyl is decreased and that of benzene is increased. An analogy recently was discovered using bromobenzene and methanol (Pd, $CaCO_3$) as reducing agent (10).

Under these conditions ("B") aromatic-aldehyde mercaptals and aromatic-ketone mercaptols give low yields of stilbenes only:

$$C_6H_5CH(SC_2H_5)_2 \;\begin{matrix}\xrightarrow[69\%]{\text{"A"}} \\ \xrightarrow[35\%]{\text{"B"}}\end{matrix}\; C_6H_5CH{=}CHC_6H_5$$

A low yield of <u>trans</u>-dimethylstilbene is obtained with trithioacetophenone (I) in ordinary R-Ni and xylene (11). Bergmann noted this type of reaction also (12). The low stilbene yields are attributed to hydrogenolysis caused by excess hydrogen (see equation directly above). The reaction similarity between trithioacetophenone (I) and acetophenone diphenylmercaptol (II) is shown structurally: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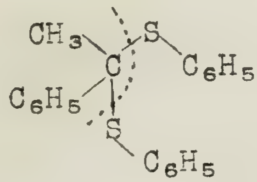
II

Thiobenzoates in the presence of "A" give mixed sulfides:

$$C_6H_5\text{-CO-S}C_6H_5 \xrightarrow{\text{"A"}} C_6H_5SC_6H_5 \quad 71\%$$

The high yield suggested that both phenyl groups take part in the sulfide formation:

$$C_6H_5\text{-CO-S-}\alpha\text{-naphthyl} \xrightarrow{\text{"A"}} \left.\begin{array}{l} C_6H_5SC_6H_5 \quad 22\% \\ C_6H_5\text{-S-}\alpha\text{-naphthyl} \quad 52\% \\ (\alpha\text{-naphthyl})_2S \quad 19\% \end{array}\right\} + CO$$

The evolved CO reduced palladium chloride to the metal.

If the sulfur is attached to a group other than aromatic, a binuclear hydrocarbon forms instead of a dialkyl sulfide (see mercaptal series above):

$$C_6H_5\text{-CO-S-}CH_2C_6H_5 \xrightarrow{\text{"A"}} \begin{array}{l} (C_6H_5)_2S \quad ?\% \\ C_6H_5\text{-S-}CH_2C_6H_5 \quad 45\% \\ (C_6H_5CH_2)_2 \quad 8.4\% \end{array}$$

In the presence of "B" aromatic thioesters yield binuclear hydrocarbons:

$$\left.\begin{array}{l} C_6H_5\text{-CO-S-}C_2H_5 \quad (28\%) \\ C_2H_5\text{-CO-S-}C_6H_5 \quad (29\%) \\ C_6H_5\text{-CO-S-}C_6H_5 \quad (46\%) \end{array}\right\} \xrightarrow{\text{"B"}} C_6H_5\text{-}C_6H_5$$

It is thus proved that the biphenyl is formed from the phenyl groups attached either to the sulfur or carbonyl group, especially since the yield is almost doubled with phenyl thiobenzoate.

Since no other products were isolated it was concluded that hydrogenolytic desulfurization also occurred.

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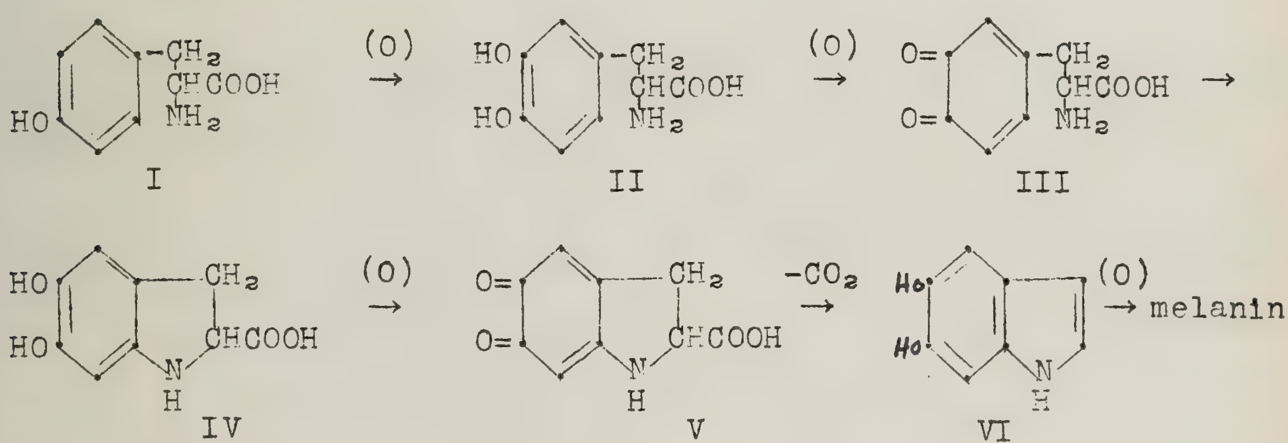
THE STRUCTURE OF MELANIN

Reported by Edward A. Sienicki April 21, 1950

Introduction: Although a great portion of the tyrosine which is ingested in the human body may be utilized for tissue structure and other purposes, the metabolism of some may result in the formation of a black pigment, melanin, which is found principally in hair, certain areas of the skin, and in the pigment layer of the eyeball. Furthermore, the darkening coloration, which is observed to take place when the skin is subjected to ultra-violet radiation, may be attributed to the increase of melanin formation in the skin (1).

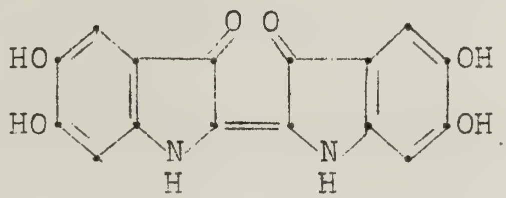
Precursors of Melanin: The enzyme tyrosinase, which oxidizes tyrosine with the formation of melanin, was discovered in 1895 by Bourquelot and Bertrand. When the enzyme acts on a slightly alkaline solution of tyrosine, a series of color changes is produced (2). The first visible color is red followed by various stages of brown until finally the black insoluble melanin is deposited. By modifying the pH of the reaction system it is possible to demonstrate three separate stages in the oxidation (3). Tyrosine gives rise to a red pigment in the first stage; in the second, this pigment is converted to a colorless substance, while in the third stage, the colorless substance is oxidized to the black melanin. The series of reactions which have been shown to take place during this transformation is shown in the following outline (4).



The conversion of tyrosine (I) into β-3,4-dihydroxyphenylalanine (II), often referred to in literature as "dopa", is found to take place readily as a result of the action of the enzyme tyrosinase. This action of the enzyme, whereby a second hydroxy group is placed on the ring ortho to the original hydroxy group, is not specific for tyrosine for it has been observed to occur with other monohydroxy phenols (5). The fact that dopa has been isolated from the reaction mixture by Raper (6) is conclusive evidence that this step does occur. The isolation of the intermediates (III and IV) has not been emphasized, for their existence seems necessary in the conversion by oxidation of dopa to 2-carboxy-2,3-dihydroindole-5,6-quinone (V). This latter compound is referred to by Raper as

the "red substance" since it is the melanin precursor which gives the red coloration to the solution (7). The existence of this quinone has been verified not only by its subsequent products but by the fact that it gives a monohydrazone with 4-nitrophenylhydrazine (4). It is believed that the carbonyl in position 5 is the one that reacts since it may be considered to be activated by the amino group in the para position. That 5,6-dihydroxyindole (VI) is a resultant product of the quinone is not disputed, for it may be isolated as the dimethoxy derivative from the red solution (8). Furthermore, it may be synthesized by a circuitous procedure which starts with 2-nitro-4,5-dihydroxybenzaldehyde (9). The product of this synthesis likewise produces melanin.

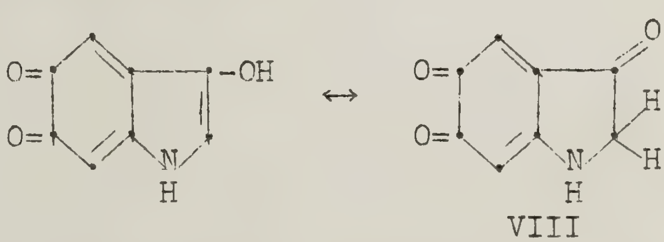
Structure of Melanin: In recent years a number of investigators (7,10,11,12) have speculated on the structure of the melanin produced from tyrosine. Clemo and Weiss, on the basis of the well known biological oxidation of indole to 3-hydroxyindole (which oxidized readily to indigo), have suggested that the conversion of 5,6-dihydroxyindole to melanin by oxidation involves the intermediate formation of 5,6,5',6'-tetrahydroxyindigo (VII) (12).



VII

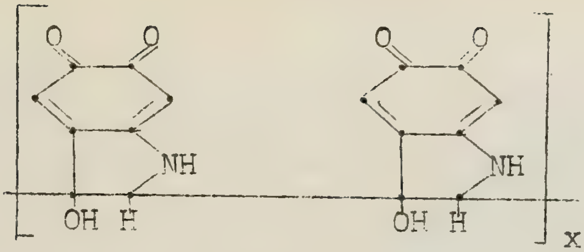
This appears to be unlikely in view of the fact that this compound, when prepared by Harley and Mason (13), did not lead to the formation of melanin.

Along a similar line, Cohen (11) has indicated that the polymerizing intermediate may be 3-hydroxyindole-5,6-quinone (VIII) which would have a reactive methylene group and might therefore be capable of self-condensation.



VIII

He does not explain the manner in which a polymeric melanin would form, but on the basis of the monohydrazone of the "red substance", one may speculate that the condensation occurs between the active methylene group and either the 5 or 3 keto group. In the latter case, the polymer fragment would appear as (IX):



IX

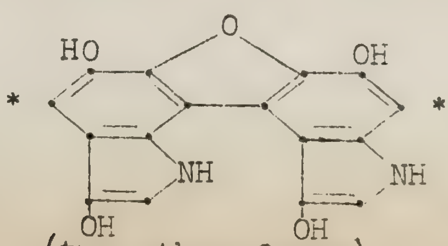
Facts in favor of such a representation of melanin are: (a) The condensation between active methylene groups and carbonyl groups is well known. Although water is often eliminated in the process, the condensation of any 2-substituted-indole (9) would of necessity prevent such elimination; (b) From Raper's investigatigation of the process taking place in the last stage of the formation of melanin (the conversion of 5,6-dihydroxyindole to melanin) it appears that two atoms of oxygen per molecule of indole derivative are utilized (3). Whether they both remained in the molecule or only one of them is fixed could not be determined. Nevertheless, IX does account for the uptake of that amount of oxygen; (c) The residual quinoid structure of the molecule may well account for the color of melanin, since the quinoid group is recognized as chromophoric. One disadvantage to this formulation of melanin, however, is that it does not agree with the analytical results for melanin as obtained by Burton (14).

Mason (7) has shown that 5,6-dihydroxyindole is readily oxidized in the presence of tyrosinase and that the most probable product should be indole-5,6-quinone. Since such a molecule possesses the quinone, amine, and pyrrole functions and since there is considerable evidence establishing the reactivity of quinones with amines and pyrroles (15,16), he concluded that it was reasonable to regard indole-5,6-quinone as a bifunctional monomer capable of undergoing coupling with itself. This conclusion contradicts the results of both Burton (14) and Raper (3).

Burton (14), in a study of the melanins formed by tyrosinase from tyrosine and β-3,4-dihydroxyphenylethyl-N-methyl amine, found that the analytical results were:

N-Methylmelanin	C - 63.1%	H - 4.1%	N - 7.8%
Melanin	C - 62.0%	H - 3.4%	N - 9.1%

In the case of N-methylmelanin the results approach a structural unit of $C_{18}H_{14}O_5N_2$ while in the latter case $C_{16}H_{10}O_5N_2$ appears to be the unit. Since the two units differ only by C_2H_4, two indole nuclei must apparently constitute a portion of each unit. As a result, Burton has postulated the diphenylene oxide structure (X) as being a possible intermediate in the formation of melanin (12).



X

(two other forms)

Such a dehydrogenative coupling as is required to form this unit is similar to that of hydroxyquinols reported by Erdtmann (17). The further polymerization of such units is difficult to envisage unless dehydrogenative coupling continues to occur at the positions in formula X which are marked by an asterisk. If such is the case, then the analytical unit should approach $C_{16}H_8O_5N_2$ rather than $C_{16}H_{10}O_5N_2$. A further disadvantage to X is that the color of melanin must then be attributed to chromophoric groups other than the quinoid group. The most favorable aspect for such a structure is that it accounts for the formation of similarly constituted melanins from 5,6-dihydroxy-1- and -2-methylindoles as well as from 5,6-dihydroxyindole itself (12).

Conclusion: Apparently the analysis of animal melanins has yielded different results according to their source. Furthermore, there is not, at present, a satisfactory criterion of their purity since the melanins are amorphous and difficult to purify. Therefore, any structure that may be proposed for the melanins must conform to the facts of previous investigations or otherwise account for any discrepancy.

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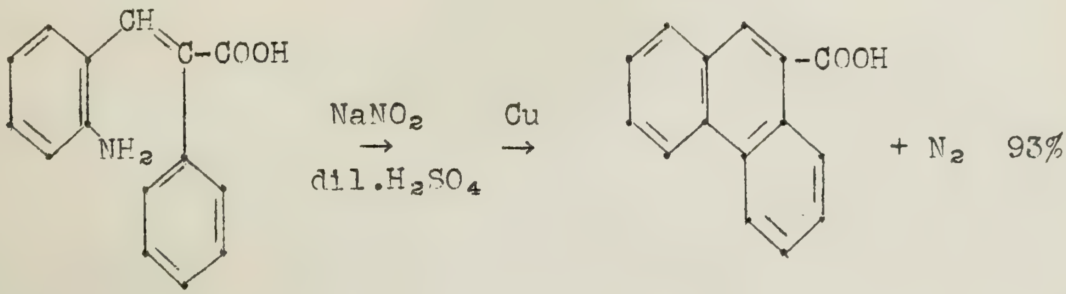
NEW APPLICATIONS OF THE PSCHORR REACTION

Reported by Victor Tullio April 21, 1950

The Pschorr reaction has been used in the preparation of phenanthrene derivatives. It involves coupling of aromatic rings by means of a diazotization reaction followed by loss of nitrogen.

Pschorr's original method (1) involved the decomposition of the diazonium salt of an o-aminostilbene, such as I, in sulfuric acid by means of copper powder at room temperature.



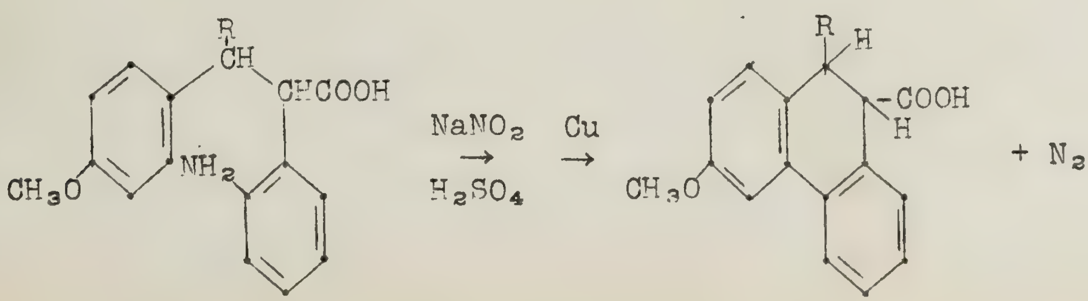
I II

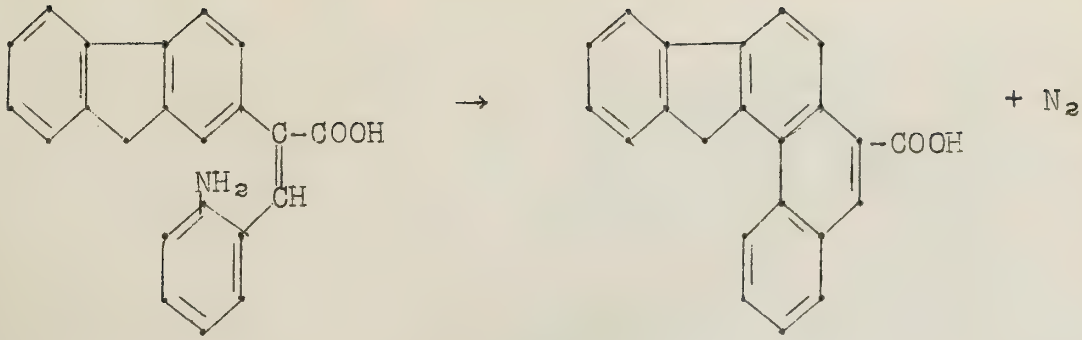
Ruggli and Staub (2) showed that the Pschorr reaction took place only when the stilbenes used were of the cis configuration. In the trans compounds, the aromatic rings are too far removed to permit coupling to take place. Luckily, in the preparation of I from o-nitrobenzaldehyde and phenylacetic acid, the cis isomer is the only one formed.

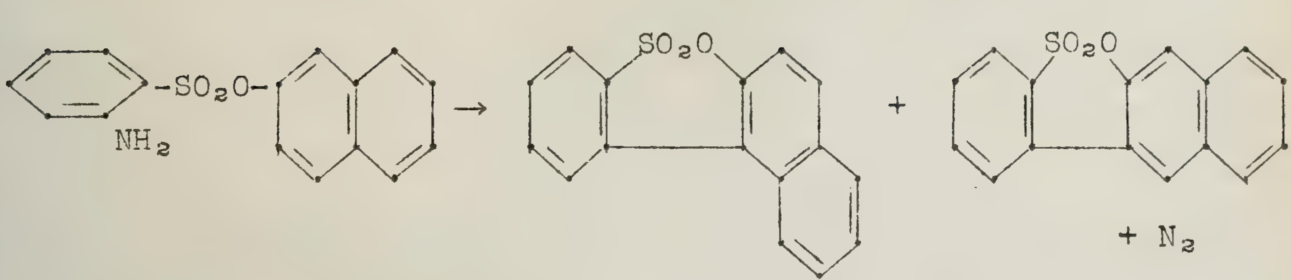
Many modifications of the diazotization and coupling procedure have been used, especially where there is a tendency for the hydroxy compound to form at the expense of ring closure. Ruggli and Staub found that in the conversion of o-aminostilbene to phenanthrene, the yields varied with the technique used.

(a) Diazotize in aqueous solution; then decompose with copper powder. Yield 60%.
(b) Diazotize in alcohol solution using amyl nitrite; then add copper powder. Yield 64%.
(c) Same as (b), but using sodium hypophosphite with the copper. Yield 80%.

The Pschorr reaction has been extended to (d) the dibenzyls, (e) fluorenylcinnamic acids (3), and (f) the preparation of cyclic sultones (4).

(d) 

(e) 



There is a similarity between the Pschorr reaction and intermolecular coupling reactions involving loss of nitrogen, such as those of the Gomberg-Bachmann type.

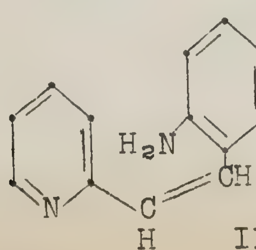
$$m\text{-}NO_2C_6H_4\overset{+}{N_2}\overset{-}{Cl} + C_6H_6 \xrightarrow[\text{rm. temp.}]{\text{alk.}} m\text{-}NO_2C_6H_4\text{-}C_6H_5 + N_2 \quad 40\%$$

$$p\text{-}CH_3CON(NO)C_6H_4N(NO)COCH_3 \xrightarrow{2C_6H_6} p\text{-}C_6H_5\text{-}C_6H_4\text{-}C_6H_5 + 2N_2 \quad 70\%$$

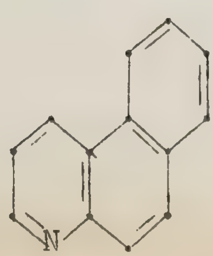
The Gomberg-Bachmann reactions proceed via a free radical mechanism, and can also be used to prepare arylpyridines, arylthiophenes, arylpyrroles, and arylfurans (5).

Since it is postulated that the Pschorr synthesis is also a free radical reaction, Hey and Osbond (6) decided to apply the Gomberg-Bachmann techniques to the Pschorr reaction, involving ring closure with a heterocyclic nucleus for the first time. In preliminary work, they applied these techniques to I. By neutralizing the aqueous diazonium salt by slow addition of an equivalent quantity of aqueous sodium hydroxide at 0°, they obtained an 81% yield of II. Decomposition of the N-nitrosoacetamido derivative of I afforded a 43% yield of II.

These techniques were then applied to III, but all attempts to produce IV were unsuccessful.

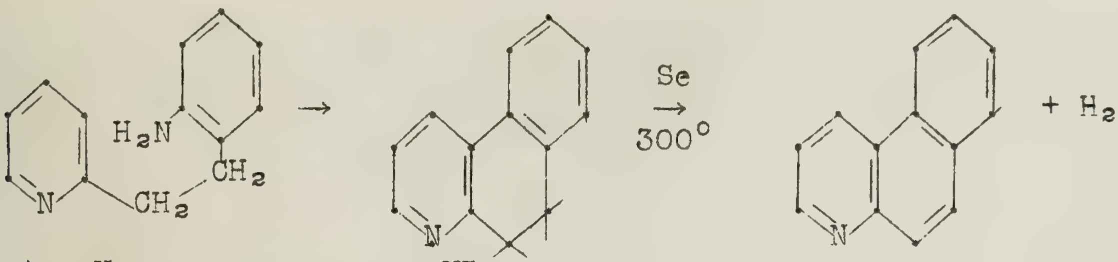


III



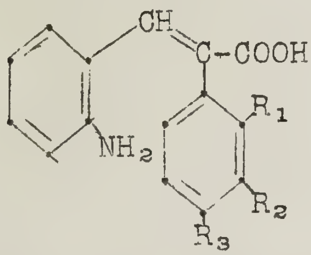
IV

It was found that in the preparation of III from α-picoline and o-nitrobenzaldehyde, only the trans isomer was formed. To overcome this difficulty, V was used as the starting material. When Pschorr's original method was used, only small amounts of the desired product were isolated. However, VI was obtained in 41% yield with the N-nitrosoacetamido method.



V VI

Hey and Osbond (7) have also carried out the Pschorr reaction with compounds of type VII where R_1 and R_3 are deactivating groups.



VII

It has been known that when R_1, R_2, or R_3 are methoxy or halogen groups, the reaction proceeds normally in good yields. Using cyano or nitro groups, Hey and Osbond found that the normal Pschorr product was obtained in good yields also.

These reactions in which the cyclization is not dependent on the type or position of substituent groups seem to be a further indication that the Pschorr reaction proceeds by a free radical mechanism.

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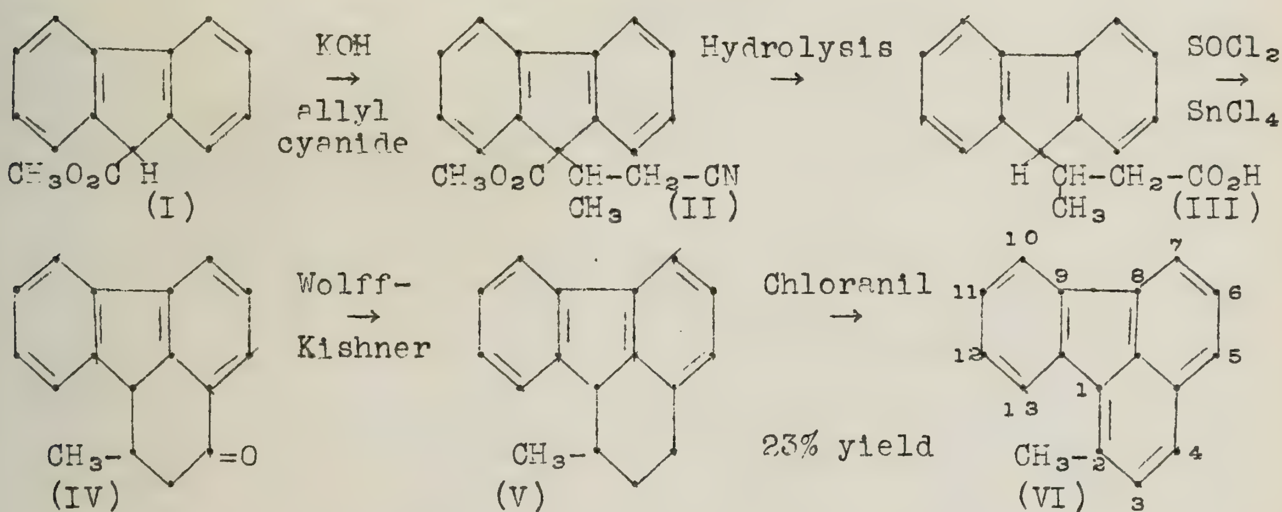
THE SYNTHESIS OF METHYLATED FLUORANTHENES

Reported by Charles F. Gilman April 28, 1950

Although fluoranthene has been known since the early days of organic chemistry, the number of its derivatives is surprisingly small (1). Of these, the most interesting from a synthetic standpoint are the alkylated fluoranthenes, investigation of which has been almost exclusively confined to compounds bearing one or more methyl radicals in positions 1-4 of the fluoranthene nucleus.

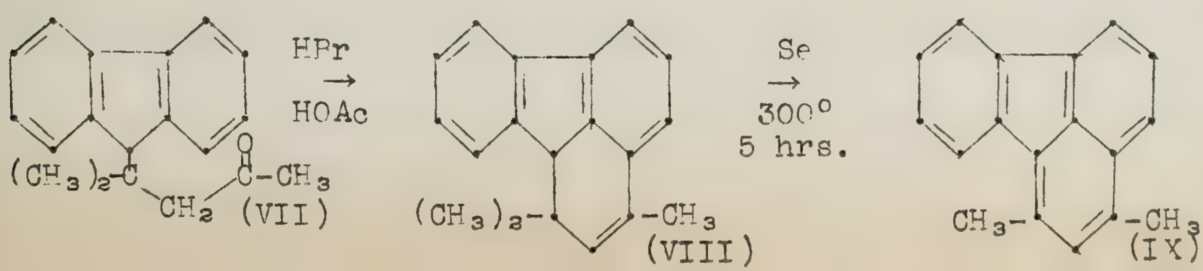
<u>Synthesis of 2-Methylfluoranthene</u>: (Method I). Methyl fluorene-9-carboxylate (I) has been used in a Michael reaction with crotononitrile (or allyl cyanide which reacts as crotononitrile under the alkaline conditions employed) to prepare 2-methylfluoranthene (VI) by the series of reactions shown below (2).



Fluorene reacts with two moles of acrylonitrile but with only one of crotononitrile (3,4). There are two advantages to the use of alkyl fluorene-9-carboxylate (I) in place of fluorene: (a) exclusive mono-addition is ensured, and (b) the available 9-hydrogen atom is rendered more reactive.

(Method 2). VI has also been prepared independently and simultaneously by a somewhat less attractive method (5).

<u>Synthesis of 2,4-Dimethylfluoranthene</u>: (Method 1). The reaction of fluorene and acetone in presence of potassium hydroxide gives rise to VII, which can be readily transformed by the action of hydrogen bromide in glacial acetic acid into VIII (6,7,8). Treatment of this with selenium removes hydrogen and methyl with the production of 2,4-dimethylfluoranthene (IX) in 25% overall yield (9).

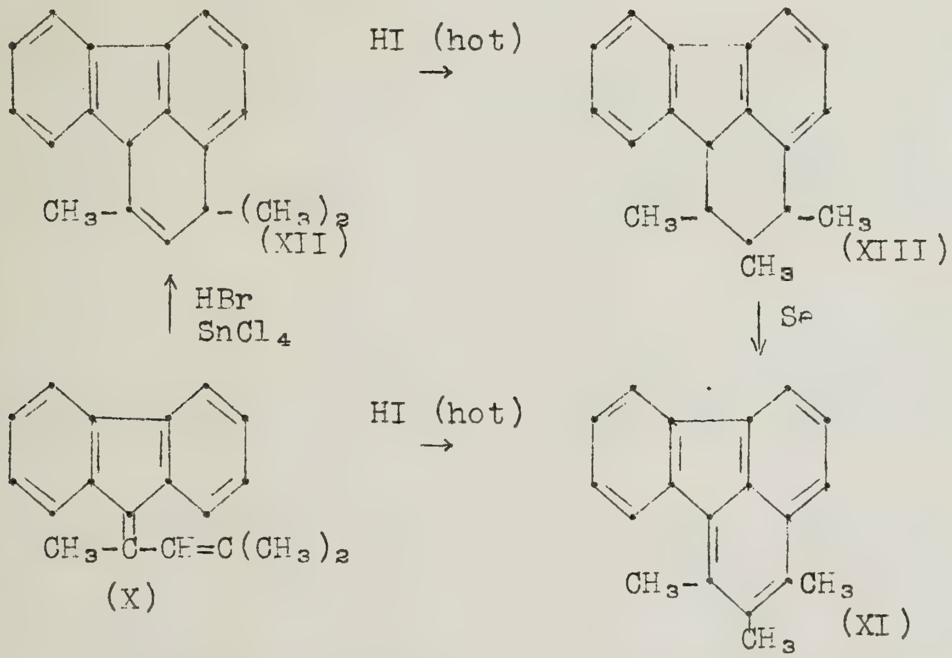


(Method 2). Methylmagnesium iodide and IV gave, without isolation of the carbinol, 2,4-dimethyl-1,2(?) dihydrofluoranthene, which by means of chloranil in boiling xylene gave 2,4-dimethylfluoranthene in an overall yield of 17% (2).

(Method 3). Treatment of XII with selenium at 300° also gives IX (10).

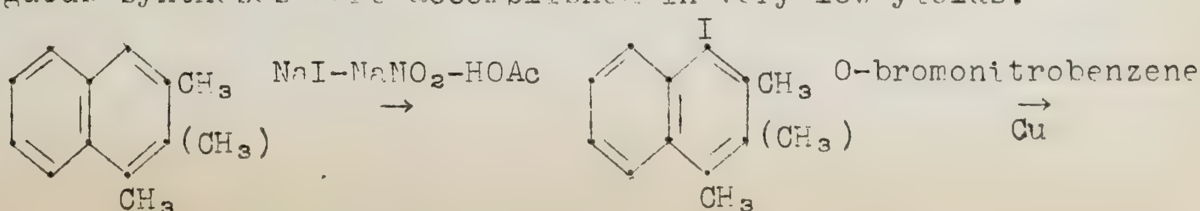
<u>Synthesis of 2,3,4-Trimethylfluoranthene</u>: (Method 1). It has been shown (6,11) that 9-fluorenylmagnesium bromide reacts with mesityl oxide to give, after dehydration, X. Among the products obtained by the action of hot hydriodic acid on X is 2,3,4-trimethylfluoranthene (XI) in 14% yield (10).

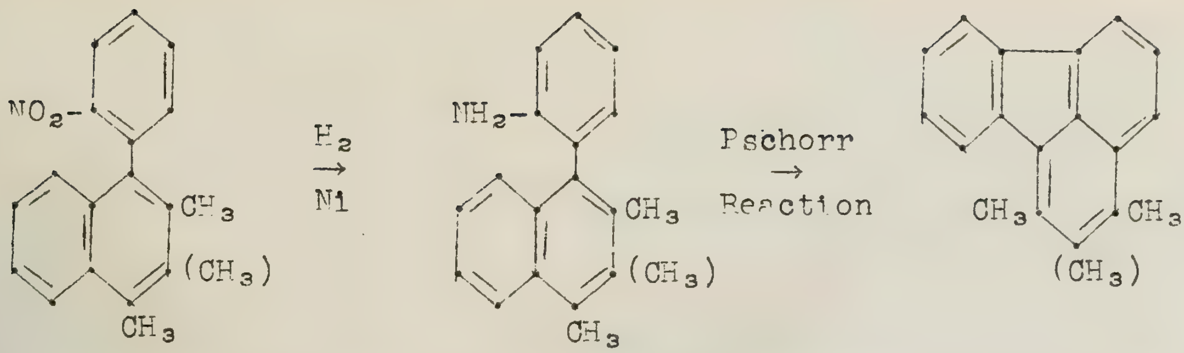
(Method 2). Treatment of X with hydrogen bromide in glacial acetic acid gave a white solid which with stannic chloride in benzene gave XII. This appears to be a new method of cyclization from an aromatic ring system possessing a butadiene side chain. Reduction of XII with a hot solution of hydriodic acid in glacial acetic acid gave XIII, which on dehydrogenation with selenium gave XI in unspecified yield (10).



(Method 3). Phosphoric oxide treatment of VIII at 250° for 90 minutes brings about migration of a methyl group with dehydrogenation, to give XI in unspecified yield. XI is also obtained when VIII is heated with anhydrous zinc chloride at 250° for 4 hours (9).

<u>Structure Proof of 2,3-Dimethyl- and 2,3,4-Trimethylfluoranthene</u>: Unambiguous syntheses were accomplished in very low yields.





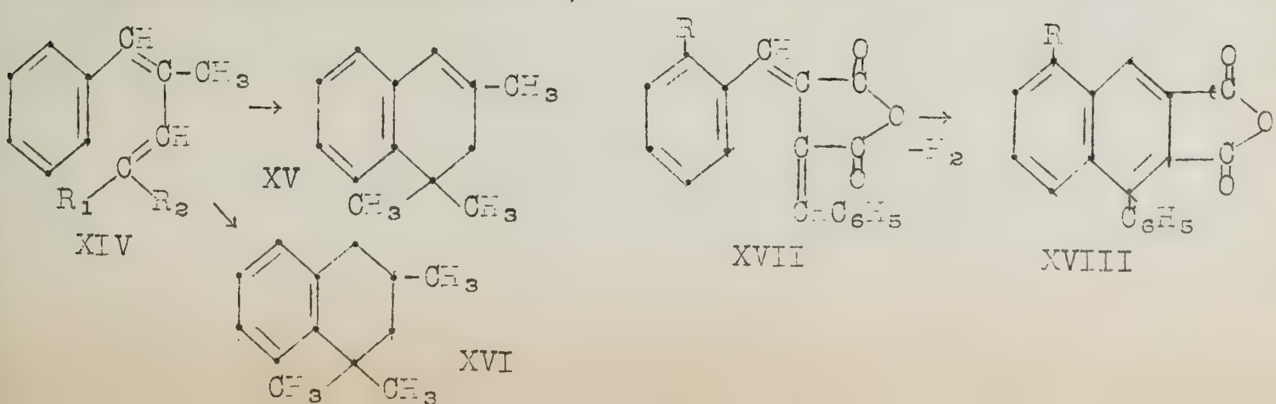
<u>Synthesis of Methylated Naphthalenes</u>: New syntheses for methylated naphthalenes were studied.

<u>(a) 1,3-Dimethylnaphthalene</u>: (Method I). 1,3-Dimethylnaphthalene has already been synthesized from <u>m</u>-xylene and succinic anhydride in yields of about 17% (13).

(Method 2). 1,3-Dimethylnaphthalene can be readily prepared by cyclization of butadiene derivatives by the method first used in the synthesis of fluoranthene derivatives (10). Mesityl oxide and benzylmagnesium chloride gives (XIV; $R_1 = R_2 = CH_3$) cyclized by either (a) treatment of its benzene solution with hydrogen bromide, followed by addition of stannic chloride, to give XV (83% yield); or, (b) by boiling with hydriodic acid in glacial acetic acid, to give the corresponding tetrahydronaphthalene (XVI). The dihydronaphthalene (XV), as also the corresponding tetrahydronaphthalene, underwent dehydrogenation-demethylation to give 1,3-dimethylnaphthalene. Overall yield by method (a) 30%; by method (b) 7% (14).

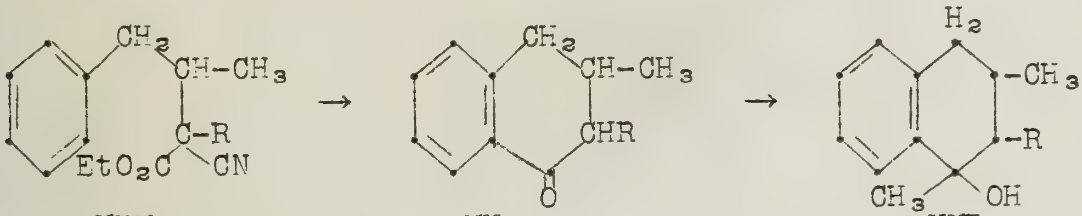
Similarly, ethylideneacetone reacted with benzylmagnesium chloride to give XIV (R_1 = H, $R_2 = CH_3$), which, by means of hydrogen bromide and stannic chloride followed by dehydrogenation, gave 1,3-dimethylnaphthalene (poor yield). Under this treatment 1-phenylbutadiene gave a polymer.

As far as the English workers are aware, the only comparable cyclization of a phenylated butadiene - and the resumblance is formal only - is the conversion of dibenzylidensuccinic anhydride (XVII) by exposure to sunlight in presence of iodine, into 1-phenylnaphthalene-2,3-dicarboxylic anhydride (XVIII). It will be noted, however, that in this cyclization a molecule of hydrogen is simultaneously eliminated (15).



XIV XV XVI XVII XVIII

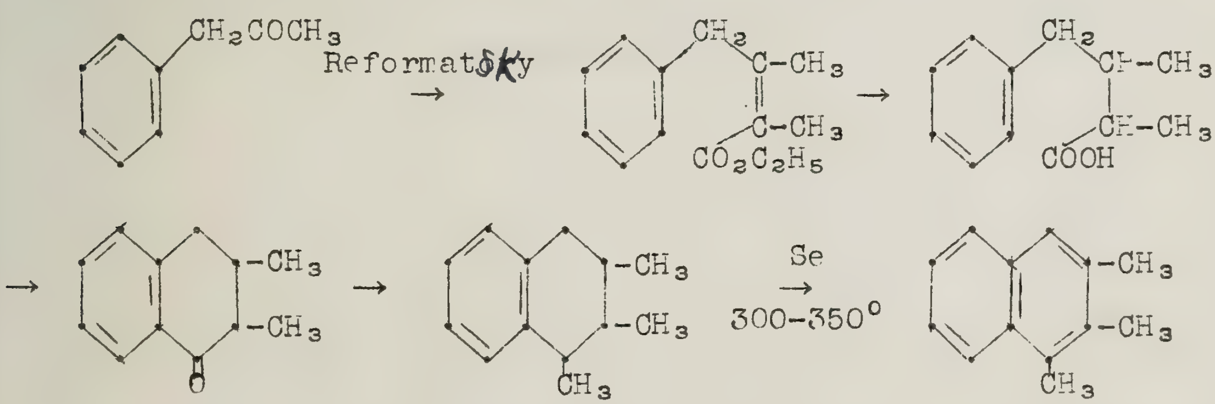
(Method 3). Another method of synthesis of 1,3-dimethylnaphthalene, which can be adapted for the synthesis of 1,2,3-trimethylnaphthalene, was suggested by the work of Cope (16) who condensed benzylmethyl ketone with ethyl cyanoacetate to give a compound which by hydrogenation gave XIX (R=H). Hydrolysis of XIX, and decarboxylation, followed by cyclization, yielded XX (R=H). The Grignard reaction on XX of methylmagnesium iodide gave XXI (R=H). Dehydration and dehydrogenation gave 1,3-dimethylnaphthalene, in 26% overall yield (14).



XIX XX XXI

(b). <u>1,2,3-Trimethylnaphthalene</u>: (Method 1). When applied to hemimellitine (1,2,3-trimethylbenzene) the succinic anhydride method described above for the preparation of 1,2-dimethylnaphthalene gave 1,2,3-trimethylnaphthalene in a very low overall yield (3%) (14).

(Method 2). A synthesis due to Ruzicka uses as starting materials benzylmethyl ketone and α-bromo propionic ester and gives 1,2,3-trimethylnaphthalene in low but unspecified yields (17).



(Method 3). The synthesis of 1,2,3-trimethylnaphthalene has been accomplished from XIX (R=H) by treatment with sodium ethoxide and methyl iodide to give XIX ($R=CH_3$). Hydrolysis and cyclization, as above, led to XX ($R=CH_3$) which, by the action of methylmagnesium iodide gave XXI ($R=CH_3$) with accompanying dehydration product. The mixture on dehydrogenation by selenium gave 1,2,3-trimethylnaphthalene (overall yield approximately 10%) (14).

(Method 4). The best synthesis, to date, appears to be the one developed by Hewett, who chloromethylated 2,3-dimethylnaphthalene (70% yield) and quantitatively reduced the product to the desired 1,2,3-trimethylnaphthalene (18).

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SYNTHETIC LONG CHAIN ALIPHATIC KETONES AND ACIDS

Reported by E. T. Houvouras April 28, 1950

Recent studies in the synthesis of long chain aliphatic ketones and acids have been made because former methods, e.g. Cd dialkyls (1) and the general β-keto ester synthesis (2) possess limitations such as availability of materials and low yields.

Bowman (3) has investigated the generation of free acylmalonic acid (II) from acylmalonic ester (I) leaving the rest of the molecule intact. Spontaneous or subsequent thermal decarboxylation of the keto acid (II) would lead to the ketone (III):

$$\underset{\text{I}}{RCOCR'(COOEt)_2} \rightarrow \underset{\text{II}}{RCOCR'(COOH)_2} \rightarrow \underset{\text{III}}{RCOCH_2R'} + 2CO_2$$

<u>Long Chain Aliphatic Ketones</u>: Acylmalonic esters (IV) are readily hydrolyzed in alkaline solution into the original components with no ketonic hydrolysis. The ketonic hydrolysis has been effected (4) using strong acids, e.g. boiling H_2SO_4-HAc solution resulting in $RCOCH_3$ where R is aromatic. This reaction failed completely when R = straight chain alkyl or for fully substituted compounds (I, R; $NO_2C_6H_4$, R'; n-Bu). The acid-catalyzed acidolysis of acyl malonic esters as developed by Bowman (3) is:

$$\underset{\text{IV}}{RCOCH(COOEt)_2} \underset{R'COOH}{\overset{H^+}{\longleftrightarrow}} \begin{matrix} R'COOEt \\ + \\ RCOCH(COOH)COOEt \end{matrix} \xrightarrow{-CO_2} \underset{\text{V }\beta\text{-keto ester}}{RCOCH_2COOEt} \underset{R'COOH}{\overset{H^+}{\rightleftarrows}}$$

$$R'COOEt + \underset{\text{keto acid}}{RCOCH_2COOH} \xrightarrow{-CO_2} \underset{\text{methyl ketone}}{RCOCH_3\ (VI)}$$

This transformation is effected by refluxing acylmalonic ester (1 mole) with propionic acid (8 moles) and H_2SO_4 (1 wt. % of reactants). Final traces of CO_2 are eliminated by treatment with 10 N H_2SO_4. Increased yields of acylmalonic esters (IV) were obtained by Bowman from EtOH-free solutions of ethoxymagnesiomalonic ester and acid chlorides, an improvement over the previous technique (4) in which free EtOH resulted in low yields.

High yields of $RCOCH_3$ (all 93% or greater) were obtained: R = <u>n</u>-heptyl, <u>n</u>-decyl, <u>n</u>-undecyl, <u>n</u>-heptadecyl, <u>n</u>-9-ketodecyl, ω-carboxyoctyl, <u>o</u>-Cl phenyl, and <u>p</u>-NO_2 phenyl.

Isolation of intermediate β-keto esters (V) from the corresponding acylmalonic esters was also investigated. Previous methods include the thermal pyrolysis of acylmalonic esters to form the corresponding acetic esters (5) and a general β-keto ester synthesis (2) using the inaccessible ethyl-tert-butyl malonate. The present method consists in refluxing the acylmalonate (1 mole) with glacial HAc (5 moles) and H_2SO_4 (0.22 wt.%). Moderate yields of the β-keto esters were obtained.

Acyl Malonic Esters (IV)	Keto Esters (V)	Methyl Ketones (VI)
1. Lauroyl malonic ester, R; $C_{11}H_{23}$	Lauroyl acetic ester (48%)	Methyl undecyl ketone R; $C_{11}H_{23}$ (41%)
2. R; $CH_2=CH-(CH_2)_8-$	Et-3 keto tridec-12-enoate (45%)	2-keto dodec-11-ene R; $CH_2=CH(CH_2)_8$(41%)
3. Octanoyl malonic ester, R; C_7H_{15}	Et-3-keto decanoate-43%	Methyl heptyl ketone 52%

Fully substituted acylmalonic esters (I, R=R'=Alkyl) resulted in no acidolysis. Bowman (6) then developed a new general synthesis of saturated ketones, $RCOCH_2R'$, consisting of the hydrogenolytic fission of benzyl acyl malonates (IX) with subsequent thermal decarboxylation of the keto acid (X) to form the ketone (XI):

$$\underset{\text{VII}}{R'\overset{Na}{C}(COOCH_2\emptyset)_2} \xrightarrow[\text{VIII}]{RCOCl} \underset{\text{IX}}{RCOCR'(COOCH_2\emptyset)_2} \xrightarrow[SrCO_3,\ <30^{\circ}C]{H_2-Pd} \underset{\text{X}}{RCOCR'(COOH)_2} \xrightarrow{-CO_2} \underset{\text{XI}}{RCOCH_2R'}$$

The sodio benzyl ester (VII) was formed in situ from the corresponding ethyl ester by treatment with Na in C_6H_6 and benzyl alcohol.

A variety of high molecular weight acid chlorides such as $C_{10}H_{21}COCl$, $C_7H_{15}COCl$, $C_4H_9CH(Et)COCl$ have been condensed with benzyl sodio ethane-1,1,2-tricarboxylate, benzyl sodio isobutyl malonate, benzyl sodio *n*-octyl malonate and benzyl sodio undecane-1,1,11-tricarboxylate followed by hydrogenation and decarboxylation to give excellent yields of keto acids or ketones.

Long Chain Aliphatic Acids: Previous methods using Cd or Zn dialkyls (1,9) are limited by side reactions, e.g. Wurtz, and raw material availability, while the β-keto ester method (7) is limited by the formation of undesired product resulting from the elimination of the "wrong" acyl group. The previous ketone synthesis of Bowman also leads to fatty acids (10):

$$\underset{\text{XII triester}}{\begin{matrix}(EtOOC)_2-CH \\ | \\ EtOOC-(CH_2)_n\end{matrix}} \xrightarrow[\emptyset CH_2OH]{Na} \underset{\text{XIII}}{\begin{matrix}(\emptyset CH_2OOC)_2-C-Na \\ | \\ \emptyset CH_2OOC-(CH_2)_n\end{matrix}} \xrightarrow[\text{XIV}]{RCOCl} \underset{\text{Keto triester XV}}{\begin{matrix}(\emptyset CH_2OOC)_2-C(CH_2)_nCOOCH_2\emptyset \\ | \\ O=C-R\end{matrix}}$$

$$\xrightarrow{H_2-Pd-C} \underset{\text{Keto triacid XVI}}{\begin{matrix}(HOOC)_2-C-(CH_2)n-COOH \\ O=C-R\end{matrix}} \xrightarrow{-CO_2} \underset{\text{Keto acid XVII}}{RCO(CH_2)_{n+1}COOH} \xrightarrow[H_2N\cdot NH_2\cdot H_2O,\ KOH]{\text{Wolff-Kishner}}$$

$$\underset{\text{Acid XVIII}}{R(CH_2)_{n+2}COOH}$$

<u>1. Preparation of Chain Extender (XIII)</u>: e.g. <u>Et heptane-1:1:7 tricarboxylate (n=6)</u>: Tetrahydropyran was acetylated, treated with sodiomalonic ester, and the resulting lactone ester hydrolyzed by $HBr-H_2SO_4$ to yield 7-bromo heptanoic acid. Esterification and reaction with sodiomalonic ester produced (XII, n=6), which was converted to the sodiobenzyl ester (XIII). Further reaction with hexanoyl chloride (XIV; $R=C_5H_{11}$) followed by debenzylation and decarboxylation led to 9-keto tetradecanoic acid (XVII, $R=C_5H_{11}$, n=6) which was reduced to myristic acid (XVIII, $R=C_5H_{11}$, n=6).

<u>2. α-ω-Dicarboxylic Esters as Intermediates</u>: Carbethoxylation of sebacic ester with Et_2CO_3 resulted in an impure product (XII, n=7). Sebacic ester and $Et_2C_2O_4$ formed the intermediate oxalo-ester which was decarbonylated by heating over powdered glass to form Et-<u>n</u>-octane-1:1:8 tricarboxylate (XII, n=7). Conversion to the sodio benzyl ester followed by reaction with myristoyl chloride (XIV, $R=C_{13}H_{27}$) ultimately led to 10-keto tricosanoic acid (85%) (XVII, $R=C_{13}H_{27}$). The latter was reduced to <u>n</u>-tricosanoic acid (XVIII, $R=C_{13}H_{27}$, n=7).

<u>3. Alternate Keto-Acid Synthesis</u>: Sebacic ester chloride was treated with benzyl sodio <u>n</u>-heptyl malonate (XIX, $R=n\text{-}C_7H_{15}$) to form the keto tri ester (XX). Debenzylation and decarboxylation led to 10-keto octadecanoic acid (XXI, $R=n\text{-}C_7H_{15}$, n=8) which was reduced to stearic acid (XXII, $R=n\text{-}C_7H_{15}$, n=8).

$$\underset{n=8}{(EtOOC)\cdot(CH_2)_n\cdot COCl} + \underset{XIX}{R-\underset{Na}{C}-(COOCH_2\varnothing)_2} \rightarrow \underset{\text{Keto tri ester XX}}{(\varnothing CH_2OOC)_2-\overset{R}{C}-\overset{O}{C}-(CH_2)_n-COOEt}$$

$$\underset{\text{Keto acid XXI}}{RCH_2CO(CH_2)_nCOOH} \xrightarrow[\text{Wolff-Kishner}]{\text{Redn.}} \underset{\text{Acid XXII}}{R(CH_2)_{n+2}COOH}$$

The debenzylation technique has several advantages: (1) Yields greater than 70% are obtained; (2) The malonic ester chain extender is purified through its crystalline tri acid; (3) The intermediate keto tri ester (XV) is rendered soluble by 3 benzyl groups so that subsequent reactions are carried out in fairly concentrated solutions.

<u>A New Olefin Synthesis: Erucic and Brassidic Acids</u>: Bowman (11,12) has applied the new ketone synthesis to the preparation of olefinic acids. Benzyl sodio undecane-1:1:11 tricarboxylate (XIII, n=10) and α-methoxydecyl chloride reacted to form 13- keto 14-methoxy docosanoic acid (XXIII, $R=C_8H_{17}$, n=10), reduced by Al isopropoxide to 13-OH 14-methoxy docosanoic acid. Treatment with dry HBr-Zn dust resulted in a moderate yield of brassidic acid (XXIV, $R=C_8H_{17}$, n=10, trans).

$$CH_3O\text{-}CHR\text{-}COCl + XIII \rightarrow \rightarrow CH_3OCHR\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2(CH_2)_nCOOH \xrightarrow[\text{2. HBr-Zn}]{\text{1. Redn.}}$$

XXIII

$$RCH{=}CHCH_2(CH_2)_nCOOH$$

XXIV

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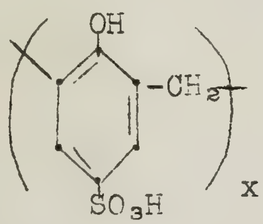
APPLICATIONS OF ION EXCHANGE TO ORGANIC CHEMISTRY

Reported by S. Gordon Smith, Jr. April 28, 1950

Although the phenomenon of ion exchange has been known for many years (1), it was not until Holmes and Adams (2), in 1935, demonstrated that synthetic ion exchange resins could be produced from the condensation products of polyhydric phenols and aromatic amines with formaldehyde that the process became of commercial interest.for processes other than water softening. Since that time many improvements in both anionic and cationic resins have been made. At the present time, ion exchange procedures are rapidly approaching unit processes in some fields.

In general, cationic resins are of three classes: those containing the -OH, -COOH, or the $-SO_3H$ group. The resins containing the latter grouping or a combination of the sulfonic acid and phenolic groups are of greatest importance. A typical resin, Dowex-30, manufactured by the Dow Chemical Company (3), has the general structure:



with some $-SO_3H$ groups replaced by methylenic cross linkages.

Anionic resins are amine-formaldehyde condensation products. m-Phenylene diamine and aliphatic polyamines have been used (4,5).

The criteria for both types of resins are, basically, a high concentration of ion-active functional groups and insolubility in water, acidic and basic solutions, and common organic solvents.

The reactions of the resins may be represented by the following equations:

(a) $2\ NaO_3S\text{-}R + CaSO_4 \rightarrow Ca(O_3S\text{-}R)_2 + Na_2SO_4$

(b) $HO_3S\text{-}R + NaCl \rightarrow NaO_3S\text{-}R + HCl$

(c) $R'\text{-}NH_2 + HCl \rightarrow R'\text{-}NH_2\cdot HCl$

where $R\text{-}SO_3Na$ represents the cationic resin on the sodium cycle, $R\text{-}SO_3H$ on the acid cycle, and $R'\text{-}NH_2$ represents the anionic resin. The latter, in most cases, behaves as an acid adsorber rather than an anion exchanger.

Although the resins are relatively expensive, the fact that they may be returned to their initial state by regeneration with sulfuric or hydrochloric acids for the cationic resin in the acid cycle, sodium chloride in the sodium cycle, and ammonium hydroxide or sodium carbonate for the anionic resin, makes their use feasible. It is somewhat limited by the desirability of water as the solvent, however.

The process of ion exchange finds its application in the field of organic chemistry as a procedure for the purification and separation of various types of compounds. It is used in three ways:

1. Removal of ionic impurities from a solution of a neutral organic compound by passing first through a cationic resin on the acid cycle, then through an anionic resin.
2. Acidic and basic compounds may be adsorbed from a solution onto anionic and cationic resins respectively. In some cases, a series of acidic or basic compounds may be adsorbed and then eluted stepwise by the use of several agents.
3. Inorganic salts of acids may be converted to the free acid with removal of the inorganic ion by passing through a cationic resin on the acid cycle.

An example of the first use, which is being used commercially in the beet sugar field, is the treatment of the raw sugar juice with a cationic resin on the acid cycle and then with an anionic resin. By this method the yield of sugar is increased, and two crops of white sugar are obtained (6). The same procedure has also been used for the production of a palatable levulose syrup from the Jerusalem artichoke (7).

The second use has found advantageous application in the separation of amino acids. They are adsorbed on the cationic resin as amine salts of the type $R\text{-}SO_3H{\cdot}H_2N\text{-}R''$, where $R''\text{-}NH_2$ represents the amino acid. Acidic amino acids are adsorbed on the anionic resin according to equation (c) (8). The latter may be separated further by a stepwise elution, using first acetic acid and then hydrochloric acid. In this manner glutamic and aspartic acids have been separated (9). Many alkaloids, such as totaquine, scopolamine, atropine, and morphine have been isolated in this way (10). The method has also been used for the separation of some naturally occurring purine and pyrimidine bases and mononucleotides (11).

The third use is mentioned because it may be of practical importance in the laboratory. Acids of a high degree of purity may be crystallized directly from the cationic effluent solution, thereby eliminating the need for repeated recrystallizations.

The procedure for setting up an ion exchange problem in the laboratory has been described by Tompkins (12).

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SUBSTITUTED ARYLSULFONYLCYANAMIDES

Reported by Virginia Menikheim May 5, 1950

<u>Introduction:</u>

Substituted arylsulfonylcyanamides are derivatives of cyanamides, $N{\equiv}CNH_2$. They may be prepared by a) the action of BrCN on a number of benzenesulfonanilides (von Braun synthesis) (1) b) the action of arylsulfonyl chloride on arylcyanamides and c) the action of excess arylsulfonyl chloride on arylureas (2). The latter, more recent, synthesis produces a wider variety of substituted cyanamides in good yield and is the reaction to be considered in detail.

<u>Course of the Reaction:</u>

$$ArSO_2Cl + Ar'NH\overset{O}{\overset{\|}{C}}NH_2 \xrightarrow[\text{low temp.}]{\text{pyridine}} \left[ArNHC\begin{matrix}\diagup O_3SAr \\ \diagdown NH\end{matrix}\right] + HCl \longrightarrow$$

$$[Ar'NHC{\equiv}N] \xrightarrow{ARSO_2Cl} \underset{O_2SAr}{\underset{|}{Ar'N}}C{\equiv}N \qquad \text{(3 and 4)}$$

An excess of arylsulfonyl chloride is desirable since the yields increase with greater molecular portions of the sulfonyl chloride.

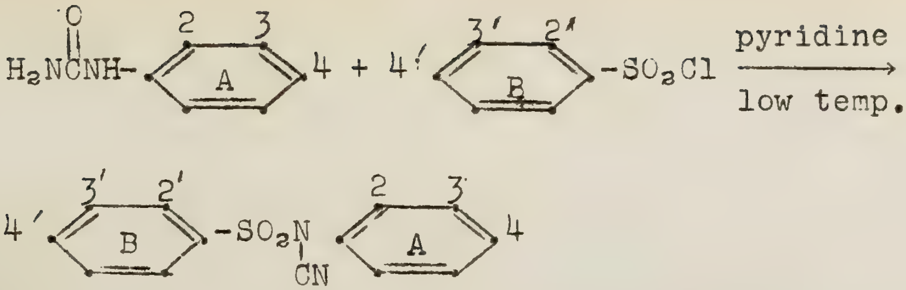
The intermediate compounds are very unstable and have not been isolated. The above course was postulated since: a) The unsymmetrical diaryl ureas form the diaryl cyanamide when subjected to arylsulfonyl chlorides under the same conditions (3).

$$ArSO_2Cl + H_2N\overset{O}{\overset{\|}{C}}NAr_2' \xrightarrow[\text{low temp.}]{\text{pyridine}} Ar'_2NCN + ArSO_3H + HCl$$

b) The symmetrical diaryl ureas do not react under these mild reaction conditions. (3) c) When substituted arylsulfonylureas, $ArSO_2NHC(=O)NHAr'$, were synthesized by an alternate method (11, 12) and treated with an arylsulfonyl chloride or other dehydrating agents under the usual mild reaction conditions, dehydration did not take place (2); therefore, the original arylsulfonyl chloride apparently did not attack the unsubstituted nitrogen, and d) the similarity to the synthesis of amidines from monosubstituted amides, sulfonyl chloride and amines for which the unstable intermediate formation of sulfonylesters $RC(=NR')SO_3R''$ was postulated. (5,6,7).

<u>THE EFFECT OF SUBSTITUENTS ON THE AROMATIC RINGS:</u>

Kruzer prepared 46 substituted arylsulfonylcyanamides, varying the substituents on the aromatic rings.



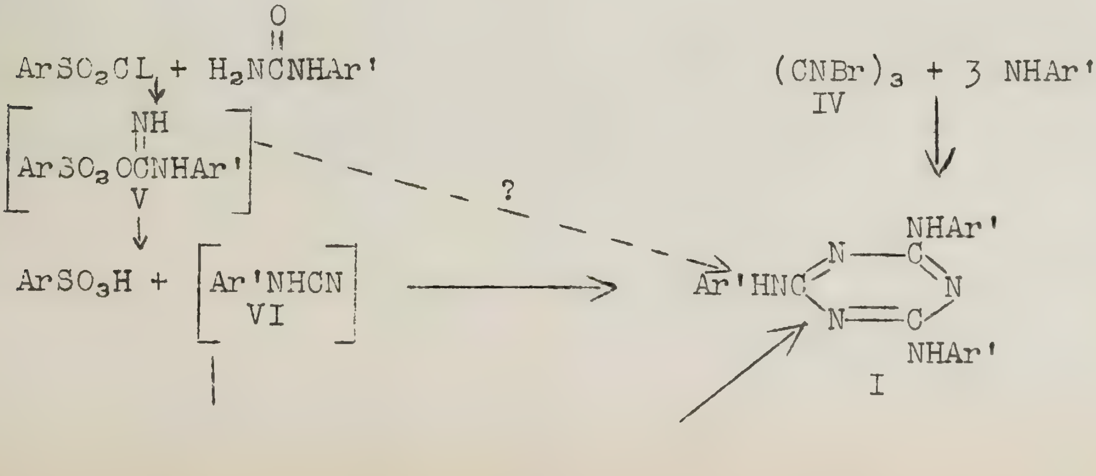
The velocity and extent of the cyanamide formation did not appear to be affected by the presence of an alkyl, phenyl, alkoxy, hydroxyl, or halogen substituted on the A ring of the above equation. Generally, yields from 70-80% were obtained, irrespective of whether these substituents were in the 2,3 or 4 position. (13).

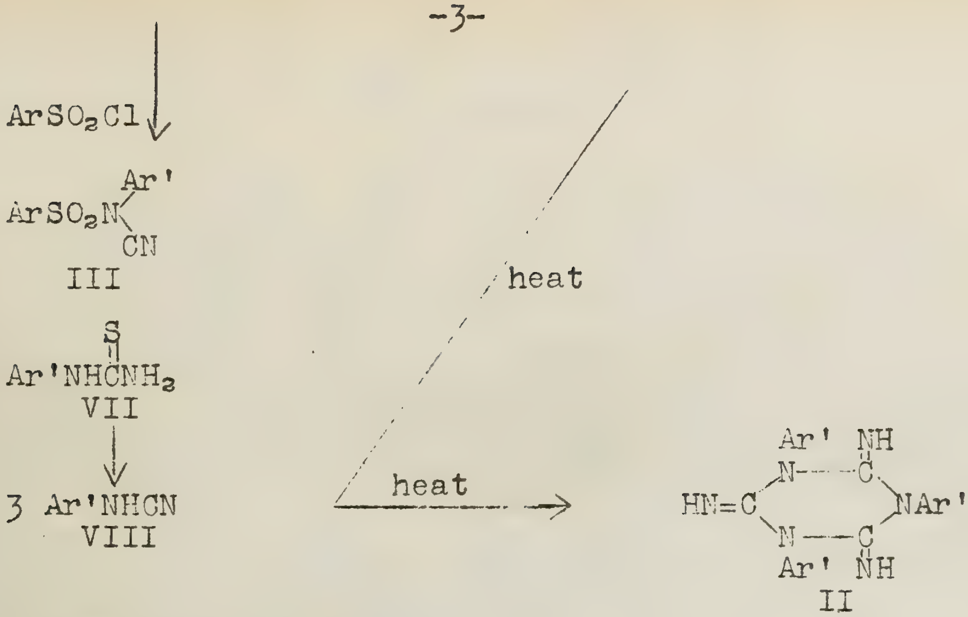
In contrast the von Braun synthesis failed entirely with the arysulfonanilides containing substitutents in the ortho position (13).

The above reaction was noticeably affected by substituents on the B ring, however. For example p-toluenesulfonyl chloride gave a 60-70% yield while o-toluenesulfonyl chloride gave only a 40-50% yield. The meta toluenesulfonyl chloride was more variable. Kruzer thought that the reduction in yield, when a substituent was present in the 2' position of the B ring, was due to steric rather than polar effects.

The presence of the hydroxyl group does not interfere with the general course of the reaction; however, with the excess sulfonyl chloride and especially if the contact time is increased, simultaneous esterification will occur. (13).

Low yields of cyanamides were obtained from the o-halophenylureas because of the formation of polymeric products. Varying quantities of substituted melamines were obtained. The trimers may become the principle product of the reaction under suitable conditions. Heat favors trimer formation and the yield of the trimers may be increased by increasing the reaction temperature.





Ar' = ortho halophenyl

The trimerization of cyanogen and its derivatives is well known. The trimers of cyanamides are classified as melamines.

The melamines (I) may be prepared by the interaction of the primary and secondary amines with cyanuric halides (IV) which are obtained by the trimerization of the monomeric cyanohalides (14).

The isomelamines (II) are generally prepared by the thermal trimerization of cyanamides (VIII) (15). Kruzer obtained (I) and a small amount of (II) from o-chlorophenylcyanamide and a mixture of I and II from o-bromophenylcyanamides.

The intermediate proposed for the general cyanamide reaction is quite satisfactory for the trimerization. Kruzer suggests that part of the arylcyanamide (VI) trimerizes before interaction with the excess sulfonyl chloride.

When o-chlorophenylurea is reacted with an arylsulfonyl chloride it forms the melamine trimer more readily than does the p-chlorophenylurea; yet p-tolyl and p-chlorophenylcyanamides undergo trimerization at ordinary temperatures in 3-7 hours while the o-chlorophenylcyanamide did not trimerize in the solid state or in benzene solution on storage at 20-30° for several weeks. The o-chlorophenylcyanamide will trimerize on heating at 100° for a short time to give a glass-like product. (2)

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CATALYTIC HYDROXYLATION OF UNSATURATED COMPOUNDS

Reported by L. Elmer Olson May 5, 1950

The direct conversion of unsaturated compounds into the corresponding α,β-glycols, usually termed "hydroxylation" has been known for some time. Omitting indirect methods, e.g. through the chlorohydrin, the methods employed may be classified as follows:

I Oxidation by permanganates, chlorates, lead tetraacetate, organic peracids, etc.

II Direct addition of hydrogen peroxide as such

A. In acetic or formic acid.
B. In an organic diluent in the presence of metal oxides, or the derived peroxy acids, capable of acting as hydrogen peroxide transfer catalysts.
C. Under the action of ultraviolet light.

This report is concerned with type IIB although the classification cannot be rigid as many interconnections exist. According to Triebs (1), as catalysts, metal oxides which easily and reversibl. form peroxy acids are required. The oxides of titanium, zirconium, thorium, vanadium, niobium, tantalum, chromium, molybdenum, tungsten and uranium give unstable peroxyacids rather than peroxides. (2). Osmium tetroxide and selenium dioxide have also been used as catalysts. Mention might also be made of various metal ions such as Fe(II) and Cu(II) to catalyze the oxidizing action of hydrogen peroxide (3).

The choice of a solvent is important because most solvents are attacked by hydrogen peroxide in the presence of catalysts. The most successful solvents are water, acetic acid or anhydrous _t_-butanol.

Recently (4) a survey of the various catalysts and their efficiency was made which may be summarized as follows:

Osmium tetroxide in _t_-butanol (not necessarily anhydrous) gave practically quantitative yields of glycerol from allyl alcohol at room temperature in 1 hour. At higher temperatures the reaction was faster but the yields lower.

Peroxytungstic acid (HWO_3OOH) in aqueous solution reacted extremely slowly with allyl alcohol at room temperature but eventually gave a 94% yield of glycerol. If temperatures of 60-70° were used the reaction was complete in two hours with yields of 80-90%.

Peroxyvanadic acid and peroxychromic acid were tried and found to be unsatisfactory as they also catalyze the "non-specific" oxidation of the product. Peroxymolybdic acid and selenium dioxide are of low catalytic activity but fairly efficient. The faint activity of peroxytitanic and peroxytantalic acids and ferrous ion are of theoretical interest only.

The use of peroxytungstic acid is new and has the advantage over osmium tetroxide in being non-toxic, easier to handle and readily obtainable in large quantities. It also gives different steriochemical addition. It is insoluble in organic solvents, however, and functions best in aqueous medium. Since hydrogen peroxide in acetic acid is a known hydroxylating agent (5) experiments were tried without the catalyst. The reaction was very slow but if excess hydrogen peroxide was used the yield was good. The results strongly suggested that peroxytungstic acid catalyzes the addition of peracetic acid to olefins but experiments in which the peracid and hydrogen peroxide were determined during the reaction failed to confirm this. The two reactions (a) peroxytungstic acid catalyzed reaction between olefin and hydrogen peroxide and (b) direct reaction between olefin and peracetic acid may be superimposed but (b) is very slow as compared to (a). It is suggested that the peracetic acid formed acts as a reservoir of peroxide protected against decomposition.

TABLE I

Addition to	Catalyst	Product	Direction of Add'n.	Reference
cyclohexene	OsO_4	cis-diol	cis	4,6
2:4 dimethyl 5,6 dihydropyran	"	cis diol	cis	7
maleic acid	"	mesotartaric acid	cis	8
fumaric acid	"	racemic acid	cis	8
diethyl fumarate	"	diethyl racemate	cis	9
cinnamyl alcohol (trans)	"	threo-stycerol	cis	10
cyclohexene	SeO_2	trans diol	trans	11
cyclohexene	peroxyvanadic acid	trans diol	trans	4
cyclohexene	peroxytungstic acid	trans diol	trans	4
maleic acid	"	racemic acid	trans	4
crotonic acid (trans)	"	erythro-dihydroxy butyric acid	trans	4

The steriochemistry of addition of the hydroxyl groups with different catalysts is of interest and reported examples are summarized in Table I. It is evident that the hydroxyl groups are added in a cis manner by osmium tetroxide and trans by other catalysts. The older view of free hydroxyl radicals cannot be maintained with the above catalysts because the complete difference in steriochemical addition with different catalysts. With osmium tetroxide it has been shown (12) that a cyclic osmic ester is formed followed by oxidative hydrolysis. With the trans hydroxylating catalysts the reaction is clean cut and stereospecific. A free radical mechanism is unlikely since a reaction can be carried out in good yields in the presence of picric acid. Organic peracids are reagents for the trans addition of two hydroxyl groups (13) but here the epoxide is an isolable intermediate in the absence of water and hydrogen ion. The mechanism by which the epoxide is formed is still unknown, but the reaction is facilitated by increased nucleophilic character of the double bond and is considered by Swern (14) to be an ionic

addition reaction. The first addition is probably that of a potential cation arising from polarization of the peracid in the sense $AcO^{-}O^{+}H$ to the electronegative side of the double bond. A similar postulate can be applied to peroxytungstic acid if this can react as $HWO_4^{-}OH^{+}$. Since hydrogen peroxide has very little tendency to react as $HO^{+}OH^{-}$ it cannot add directly to an ethylenic linkage without mediation of a catalyst.

Recently the catalytic hydroxylation of some aromatic hydrocarbons has been reported (15).

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SOME RECENT CHEMISTRY OF ETHYLENIMINE

Reported by William W. West May 5, 1950

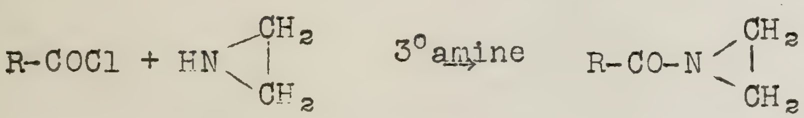
After the discovery of ethylenimine by Gabriel (1) in 1888, little work was done with this cyclic amine or its derivatives until just a few years prior to the last war, when a group of German workers under Greune became interested in ethylenimine in work connected with the improvement of artificial fibers. A recent seminar (2) has surveyed some of the preparations and properties of various ethylenimines. Since this time, a number of new reactions of the compound have been reported by Greune and his coworkers. A considerable portion of this work has been summarized by Bestian (3) in a recent article.

Ethylenimine, a low boiling and highly poisonous liquid, is prepared by the thermal dehydration of monoethanolamine sulfate which forms β-aminoethylsulfuric acid, followed by distillation with alkali (4). Like its oxygen analogue, ethylene oxide, ethylenimine shows a marked tendency towards cleavage, and in addition, the activated hydrogen of the imine ring can be replaced with a variety of substituents.

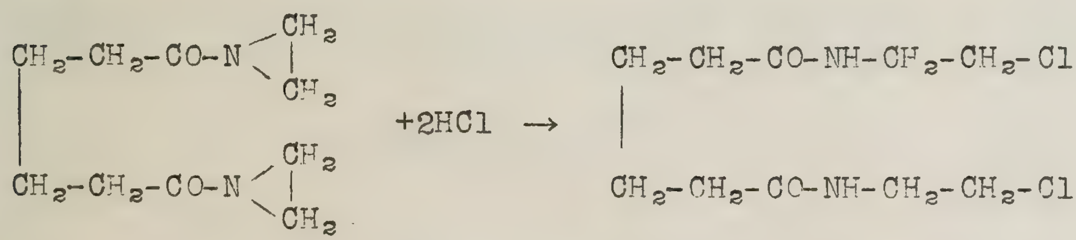
For convenience, the reactions to be described here will be divided into three classes. A fourth large group, polymerization, will not be considered.

Acylation and alkylation reactions with halogen compounds.

Acylation reactions are best accomplished by using an acid chloride in an inert solvent, along with a tertiary amine (usually triethylamine) to neutralize the hydrochloric acid formed.



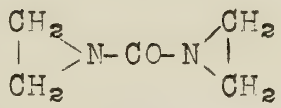
The ethylenimides of carboxylic and sulfonic acids are frequently unstable, and cannot always be purified. The diethylenimide of adipic acid (I) was obtained in good yields (3) from adipyl chloride and characteristically it reacted with excess hydrochloric acid to form the di-(β-chloroethylamide) of adipic acid (II).



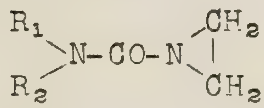
I II

Good yields of diethyleneurea (III) were obtained from phosgene and ethyleniminc (5). The acid chlorides of dialkylated carbamic acids reacted smoothly with ethylenimine to form disubstituted ethlyene-

ureas (IV) (6), and good yields of the similar cyclic product were

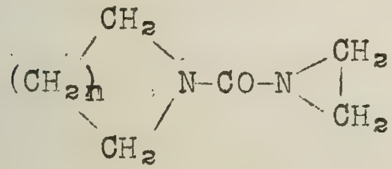


III



IV

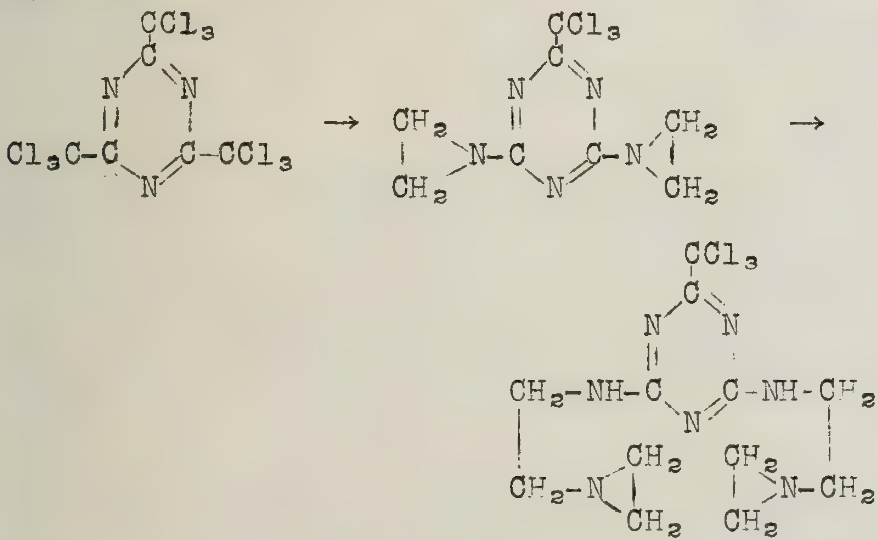
obtained from the reaction of such compounds as piperidine (7), with phosgene and ethylenimine. (V)



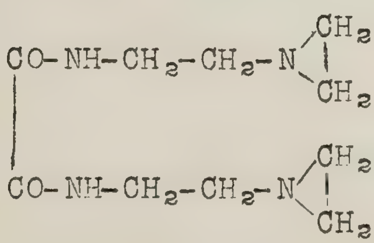
n = 2 - 4

V

All of the chlorine atoms of cyanuric chloride (8) and phosphoric oxychloride (9) are replaced by the ethylenimine ring. However, with 2,4,6-triperchloromethyl-1,3,5-triazine, a different reaction occurred:

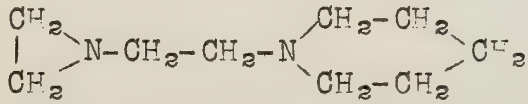


A somewhat similar situation is encountered in the reaction between ethylenimine and ethyl oxalate, in which product (VI) is formed (10)



(VI)

More extreme reaction conditions are required for alkylation reactions of ethylenimine. Thus, N-(β-ethyleniminoethyl)-piperidine (VII) is formed from N-(β-chloroethyl)-piperidine, ethylenimine and sodamide at elevated temperatures.

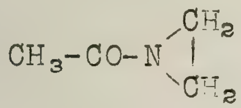


VII

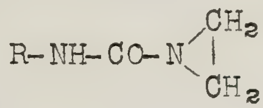
Acylation and alkylation by addition.

The addition of ethylenimine to unsaturated compounds to form N-acyl- or N-alkylethylenimides proceeds smoothly and the products formed are easy to purify.

Acetyl ethylenimide (VIII) is obtained in practically theoretical yields by adding ketene to anhydrous ethylenimine at 25° (15). Ethylenimine adds readily to isocyanates to form N,N-ethyleneureas (IX) (11).



VIII



IX

Diisocyanates and even triisocyanates have been used to form products containing two and three ethyleneurea groups.

The addition of ethylenimine to carbon-carbon double bonds forms many N-alkyl substituted ethylenimines. Such addition occurs with the esters, amides and nitriles of α,β-unsaturated carboxylic acids, as well as with vinyl ketones, vinyl sulfones and various dienes. (3).

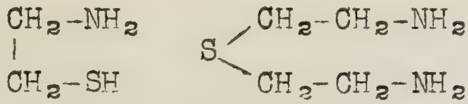
A good yield of the methyl ester of β-ethylenimino propionic acid is obtained from methyl acrylate and ethylenimine. Acrylonitrile and ethylenimine form the corresponding nitrile. Similar reactions are shown with crotonic acid. β-Ethylenimino succinic acid is formed from both ethyl fumarate and ethyl maleate. The catalytical effect of alkali metals is required for the addition to diene systems.

Ring openings.

These reactions provide a method of determining the reactivity of ethylenimine rings, and also provide some useful synthetic intermediates.

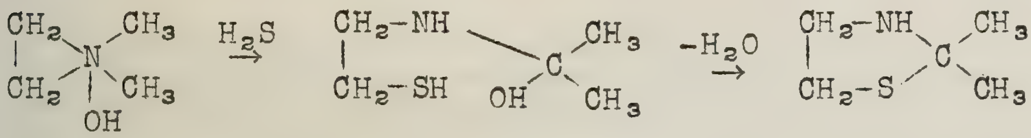
β-Mercaptoethyleneamine (X) has been made in 70-80% yields by reacting ethylenimine (in methanol) with an excess of hydrogen

sulfide at -60° (12) whereas at ordinary temperatures β,β'-diaminodiethyl sulfide (XI) is formed. (13).



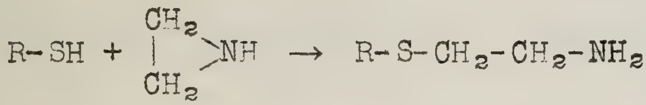
X XI

An ethylenimmonium sulfide has been postulated as an unstable reaction intermediate to account for the formation of (XI). This reaction has resulted in a new thiazolidine synthesis (14). When ethylenimine and hydrogen sulfide were dissolved in acetone, the following reaction occurred:



Using an aldehyde resulted in a 2-monosubstituted thiazolidine.

Ethylenimine reacts with mercaptans to form β-aminoethyl sulfides (3).



However, with ethyl thioglycolate, the original sulfide is easily converted at room temperature to the more stable thiazane ring in good yields.

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REACTIONS OF METHAZONIC ACID

Reported by Ernest Nicolaides May 12, 1950

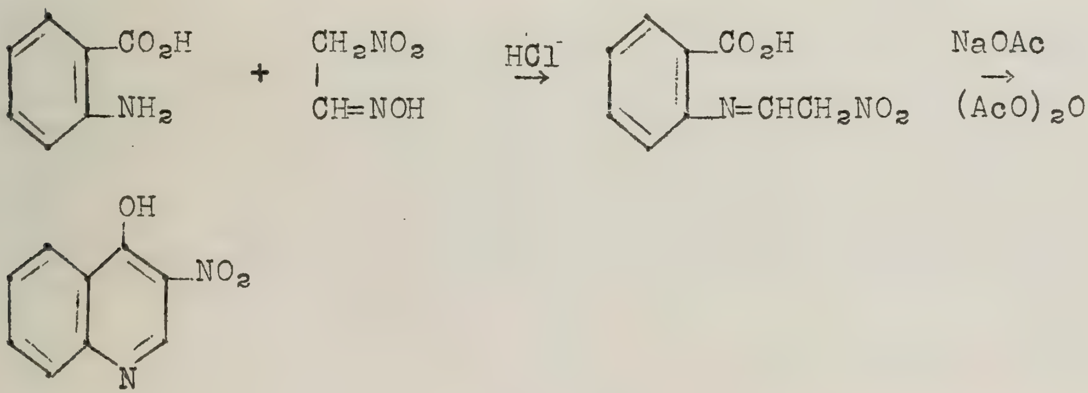
Methazonic acid (I) was first prepared by Friese in 1876 (1), but it was not until much later that the compound was identified as the oxime of nitroacetaldehyde (2). It is best prepared by the action of sodium hydroxide upon nitromethane. The free acid is obtained by acidification of the basic solution in the presence of ether. The yield is 45-50% (2,3).

$$\underset{}{CH_3NO_2} + \underset{\text{aqueous}}{NaOH} \xrightarrow{<50^\circ} \text{Na Salt} \xrightarrow[\text{ether}]{HCl} \underset{\text{I}}{\begin{matrix} CH_2NO_2 \\ | \\ CH{=}NOH \end{matrix}}$$

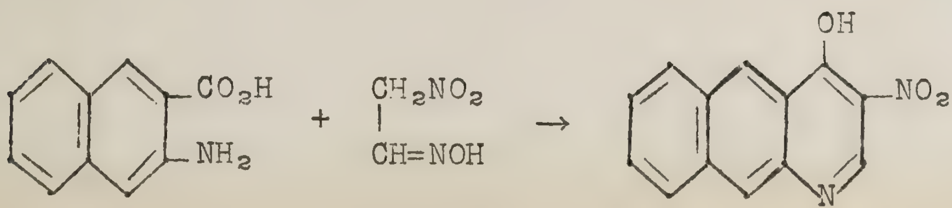
Methazonic acid reacts with aniline and its derivatives to give β-nitro ethylidenamino compounds, but its main use has been in the synthesis of 3-nitrolepidines and 3-nitroquinolines.

Previous to the methazonic acid synthesis, 3-nitroquinolines were obtained by only two methods; direct nitration of hydroxy or amino quinolines and the nitromalonaldehyde synthesis of Uhle and Jacobs (4).

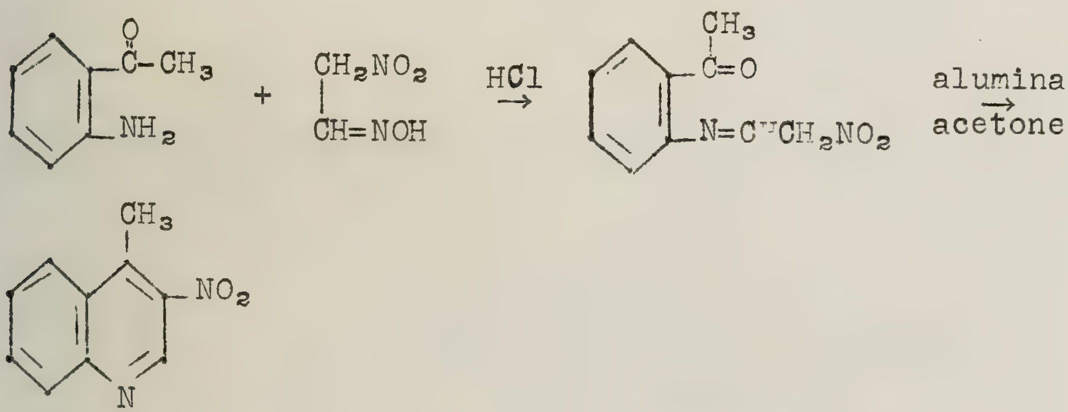
Several investigators have used the methazonic acid synthesis with anthranilic acid and similar compounds. 3-Nitro-4-hydroxy quinoline was obtained from anthranilic acid (5),



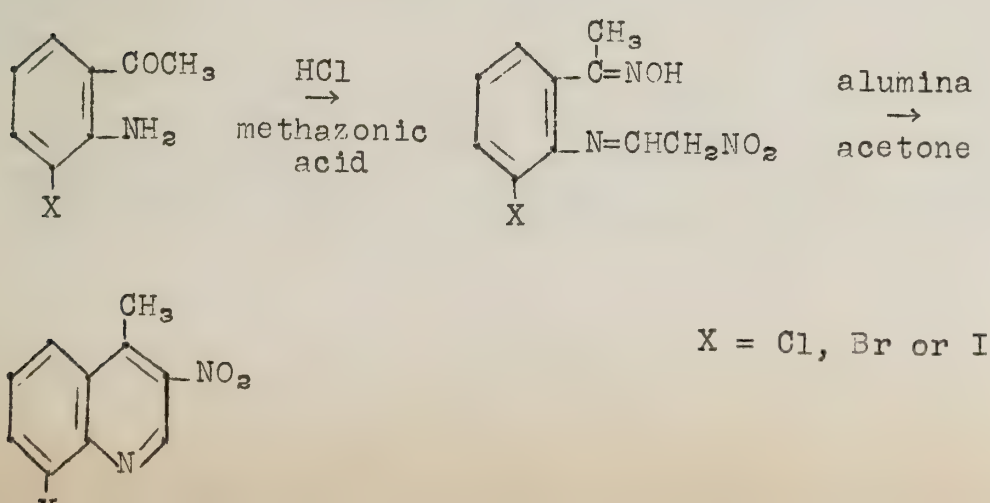
From 3-amino-2-naphthoic acid, 3-nitro-4-hydroxy-6,7-benzoquinoline was also obtained (6).



The reaction described in a German Patent (7) between o-amino-benzaldehyde and methazonic acid to form 3-nitroquinoline has been little used because of the unavailability of o-amino-benzaldehydes and the poor yields obtained. Recently, however, it has been shown that good yields of 3-nitrolepidines and 3-nitro-quinolines can be obtained from o-aminoacetophenones and benzophenones (8). It was found that the reaction proceeded in two steps instead of one as the German Patent claims. The intermediate is the β-nitro-ethylidenamino compound as in the anthranilic acid reaction. It was also found that a quantitative yield of the nitroquinoline could be obtained by using activated alumina in acetone as a cyclizing agent.

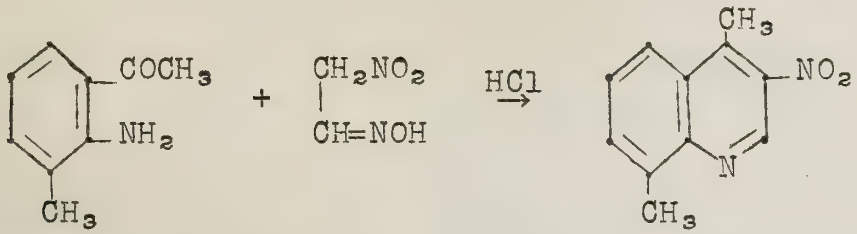


The 4,5- and 6-monosubstituted and the 4,5-disubstituted - o amino acetophenones were found to give higher yields of the β-nitro ethylidenamino compounds than o-aminoacetophenone itself. Several irregularities were also noted. The 3-chloro, bromo or iodo-2-aminoacetophenones gave a different intermediate rather than the ethylidenamino type. At present, these intermediates are believed to be the oximes of the β-nitroethyliden-amino acetophenones. These compounds can also be quantitatively cyclized with alumina to the nitrolepidines.

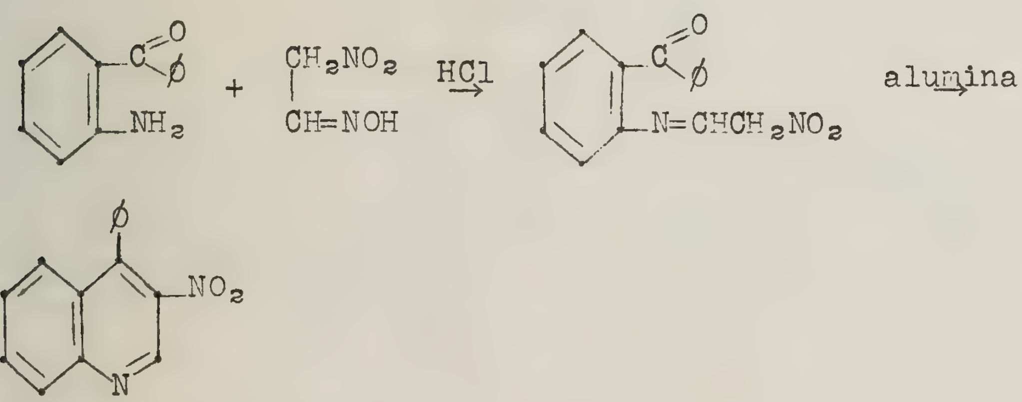


X = Cl, Br or I

3-Nitro-2-aminoacetophenone failed to react with methazonic acid, and the authors attributed this to hydrogen bonding between the nitro, amino and carbonyl groups. The 4,5 and 6-nitro-2-aminoacetophenones reacted readily, and the resulting ethylidene compounds were found to cyclize spontaneously when an attempt was made to crystallize them from acetone. 3-Methyl-2-aminoacetophenone reacted with methazonic acid to give 4,8-dimethyl-3-nitroquinoline directly.

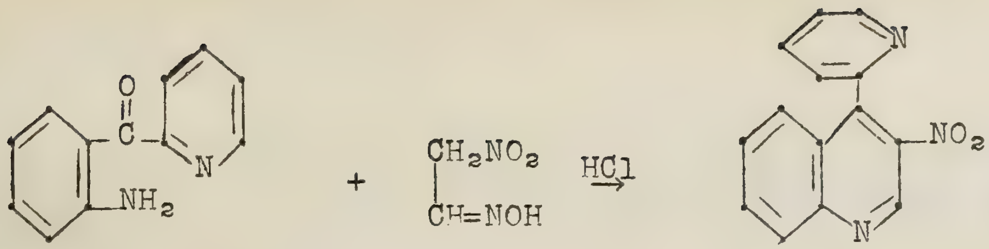


o-Aminobenzophenones also react with methazonic acid in a similar manner.

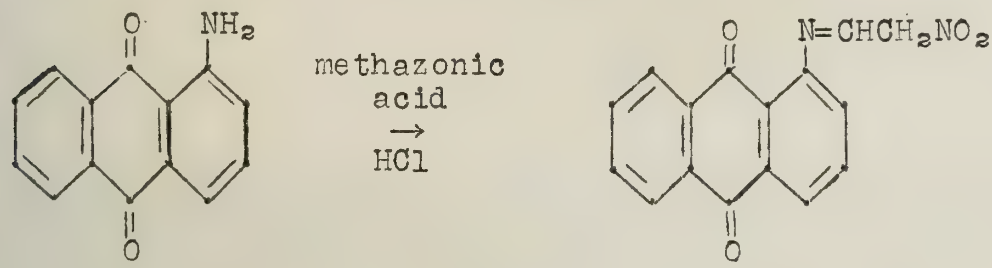


3-Nitro-2-aminobenzophenone failed to react, but the 4,5- and 6-nitro compounds reacted and survived crystallization without cyclizing. Any attempt to cyclize these nitro derivatives with alkali resulted in hydrolysis to the original amine, but again activated alumina gave quantitative yields of the dinitroquinolines.

An interesting case is that of 2[2'-aminobenzoyl]pyridine. This compound reacted with methazonic acid to give 3-nitro-4-[2'-pyridyl]-quinoline directly. This reaction is believed to be due to the increased electrophilic activity of the carbonyl group caused by protonization of the pyridyl nitrogen atom in acid solution.



α-Aminoanthraquinone and methazonic acid react in acid solution to give β-nitroethylidenamino anthraquinone, but so far no method has been found to cyclize this compound.



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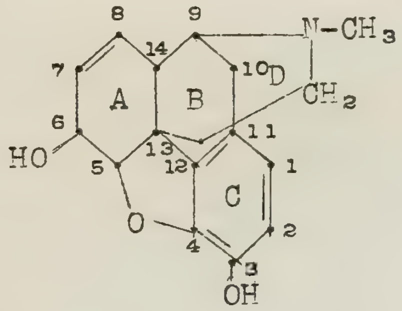
AN APPROACH TO THE TOTAL SYNTHESIS OF MORPHINE

Reported by Seemon H. Pines May 12, 1950

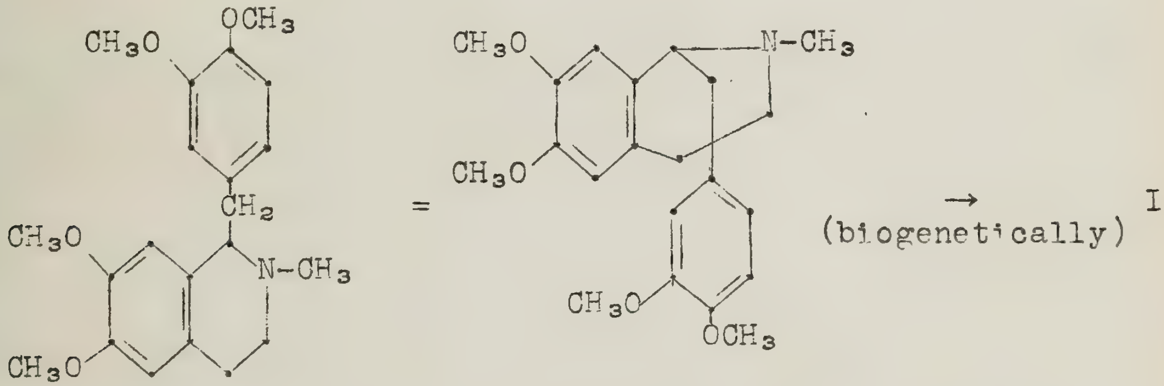
The synthesis of morphine (I) is one of the oldest problems of organic chemistry. Morphine was first isolated in 1806 by Sertürner as a crystalline alkaloid from the opium poppy (1).



Morphine (I)

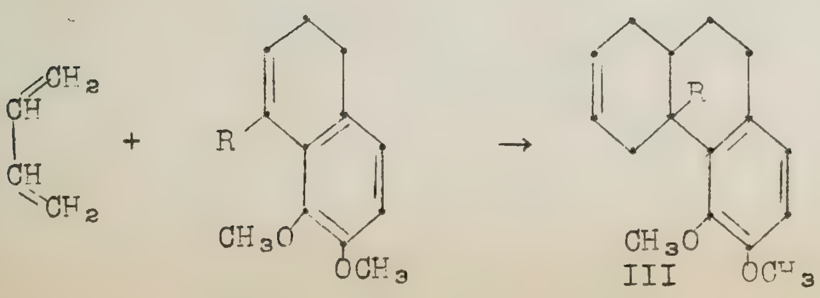
The following structural characteristics are obvious: (1) The basic skeleton of the molecule is the phenanthrene ring; (2) Positions 9 and 13 are bridgeheads for an external heterocyclic (six-membered) ring; (3) Positions 4 and 5 are joined by an oxide linkage; (4) A phenolic -OH is located at C_3; (5) A secondary -OH is located at C_6; (6) The double bond (7-8) is olefinic; (7) The nitrogen atom is tertiary; (8) C_{13} is quarternary.

Laudanosine (II), also isolated from the poppy, provides a clue to the manner in which morphine is formed in nature.



II

Early work in the field of morphine chemistry led to the synthesis of phenanthrene systems with a quarternary C_{13}. Fieser (2) carried out a Diels-Alder reaction with butadiene and 1,2-dimethoxy-5,6-dihydro-8-naphthalene carboxylic acid to give IIIa.

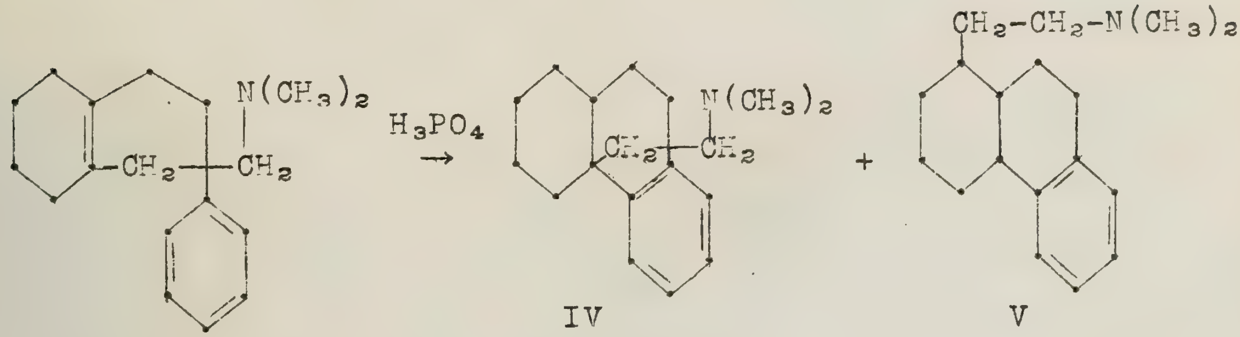


IIIa. R = -COOH

IIIb. R = $-C_2H_5$

Robinson (3) synthesized the analogous IIb.

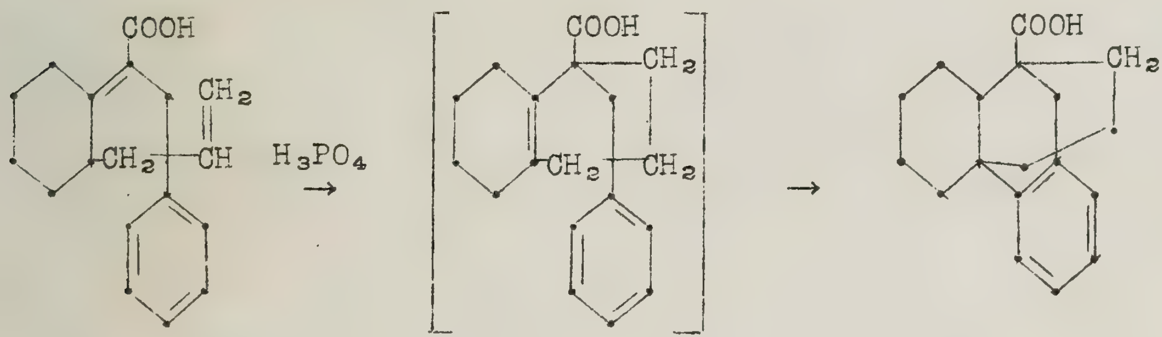
Grewe's (4) early work consisted of an approach to the same structures by a different means.



IV minor product V major product

He explained the presence of V by rearrangement of the double bond and ring closure on the less hindered α (to the side chain) position. The structure of IV was proven by quantitative aromatization to phenanthrene; V by dehydrogenation and deamination to 1-ethyl phenanthrene.

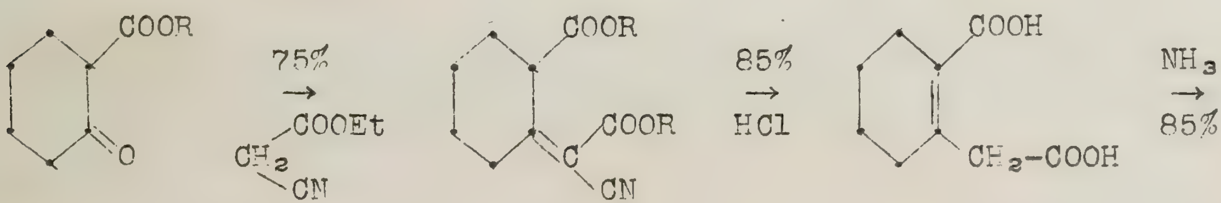
A carbocyclic analogue of the morphine system was synthesized in a similar fashion:

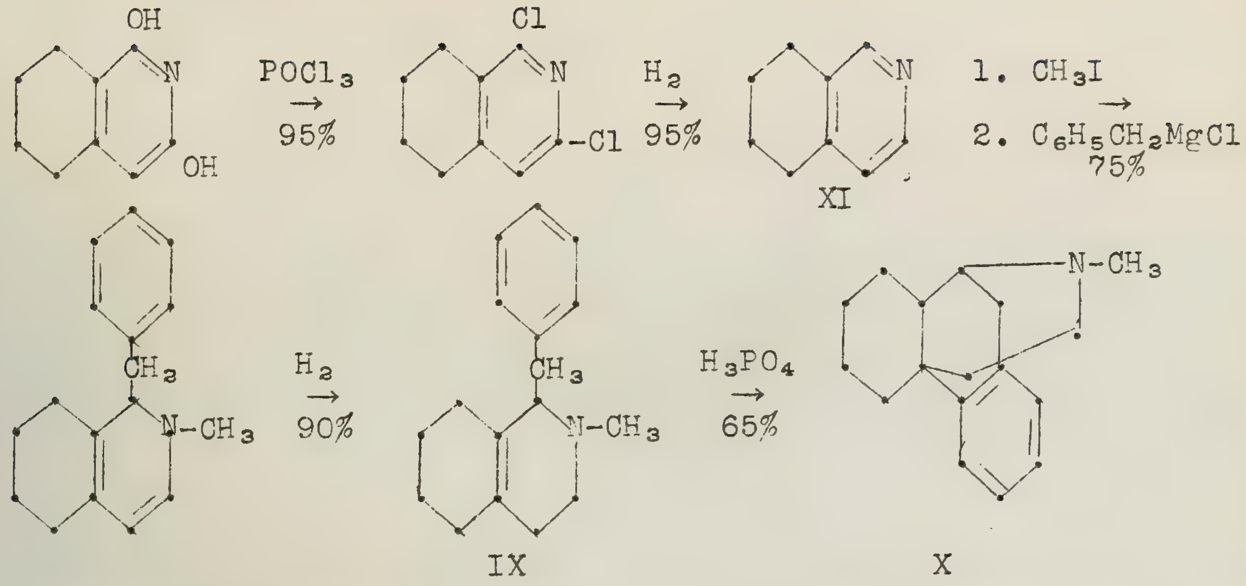


VI VII VIII

VII could not be isolated.

Morphane (X) was formed by H_3PO_4 ring closure of 1-benzyl-N-methyl 1,2,3,4,5,6,7,8-octahydroisoquinoline (IX). Below is shown the total synthesis of morphane, as carried out by Grewe.

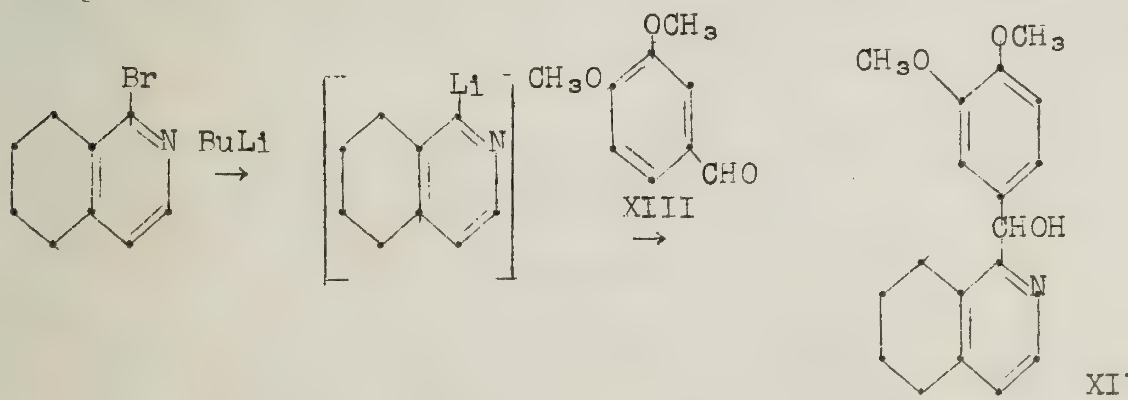




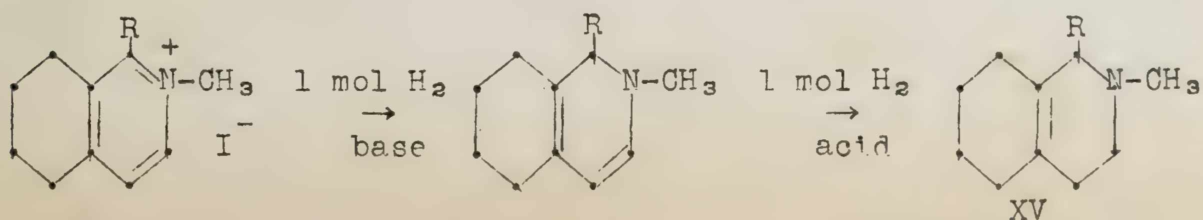
From one kg. of cyclohexanone carboxylic ester was prepared over 200 grams of pure morphane. The overall yield exceeds 17%.

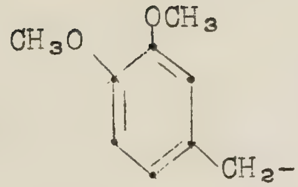
In his latest work, Grewe (5) has synthesized tetrahydrodesoxycodeine (XII), a degradation product of morphine.

Starting with B_z-tetrahydroisoquinoline (XI), the 1-bromo derivative was formed by amination with $NaNH_2$ (85%), and subsequent replacement of the amino group by Br (78%) in the manner indicated for 2-bromo pyridine (6). An exchange reaction with butyllithium was carried out at -35° in ether, and to this typically reddish brown solution was added veratraldehyde (XIII). The usual color change was observed in formation of the carbinol XIV.

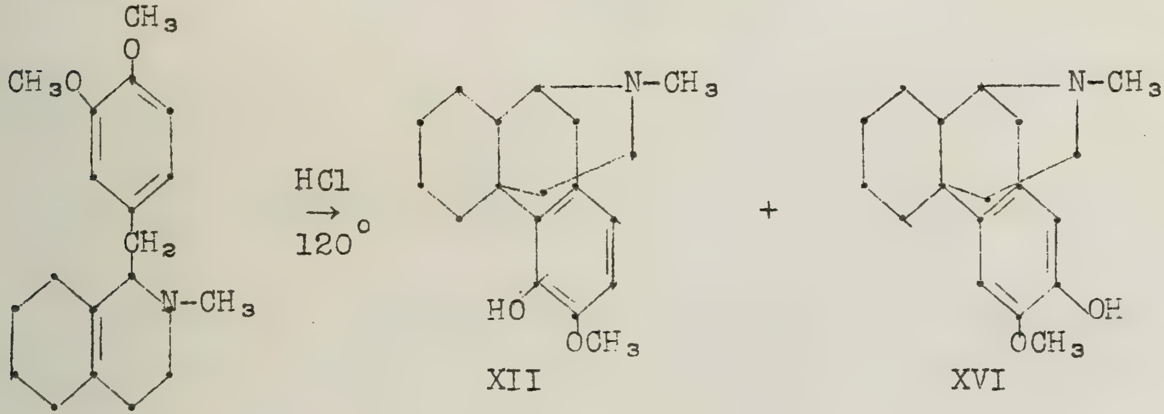


This carbinol can be reduced directly with Zn, HBr, and HOAc, or oxidized to the ketone and reduced by means of the Clemmensen. The methiodide of XIV can be catalytically reduced in a stepwise fashion to produce XV.



R = 

H_3PO_4 will not serve satisfactorily for the ring closure. HBr, in all cases, brings about cleavage of the methoxyl groups as well as ring closure. HCl can be controlled to some extent in producing the desired compound; however, a mixture of isomers and some demethylated products are obtained. The separation of the products is tedious, involving the use of dilute base, picric acid, diazomethane, etc., to provide complete separation of XII and XVI.



Configuration was assigned to the two products on the basis of the following: (1) Reaction with dilute base. XII will not dissolve, XVI will. (Steric effect of ring A.); (2) Gibb's test for phenol with unsubstituted para position. XII gives positive characteristic blue color; (3) reaction with CH_2N_2. XII negative, XVI reacts.

Finally XII was resolved by means of active tartaric acid to produce an optically active isomer identical to tetrahydrodesoxycodeine obtained from morphine degradation.

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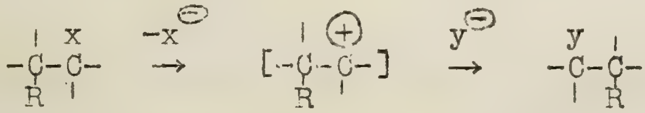
STEREOCHEMICAL STUDY OF THE WAGNER-MEERWEIN REARRANGEMENT

Reported by Robert C. Sentz May 12, 1950

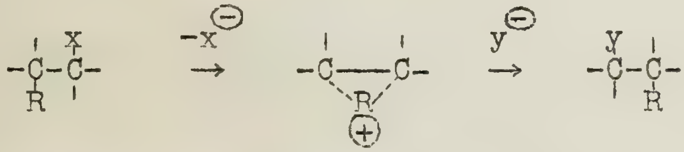
Fundamental Question: One of the basic questions in Wagner-Meerwein rearrangements of the type



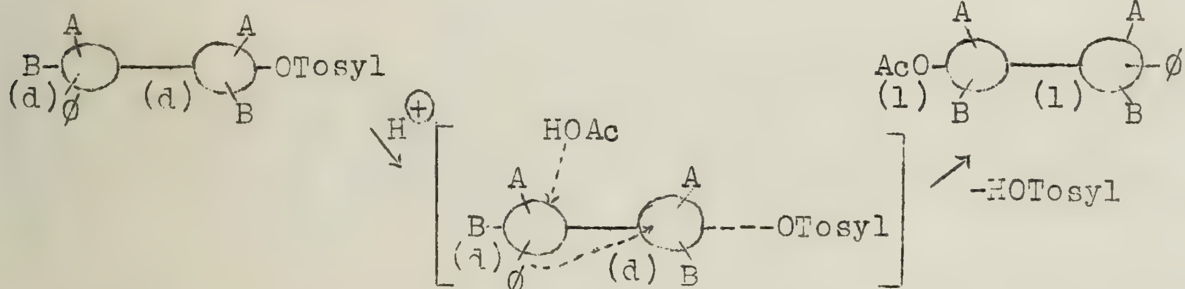
(x = or ≠ y)

has been; A. Is the process completely concerted?

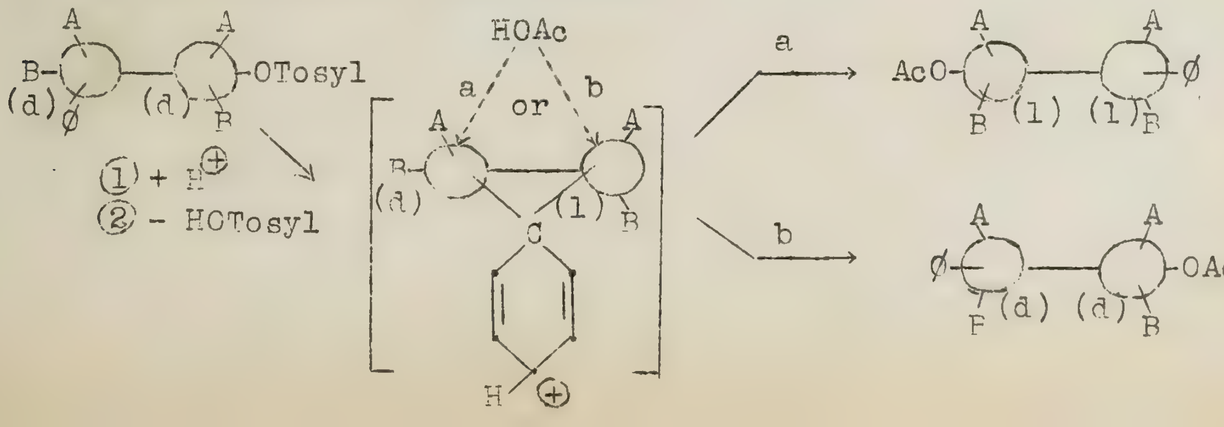
or B. Is there a stable, discrete, cyclic carbonium ion intermediate?



Cram (1) has shown that it is possible to decide between the two by a study of stereochemistry when both carbon atoms concerned are asymmetric. Thus the steric consequence of path A could only be inversion of both carbons.



Similarly it is a consequence of B that the process must involve; 1. The inversion of one carbon (the incipient carbonium carbon) during ring formation. 2. Ring opening (with inversion) at either of the two asymmetric carbon atoms.



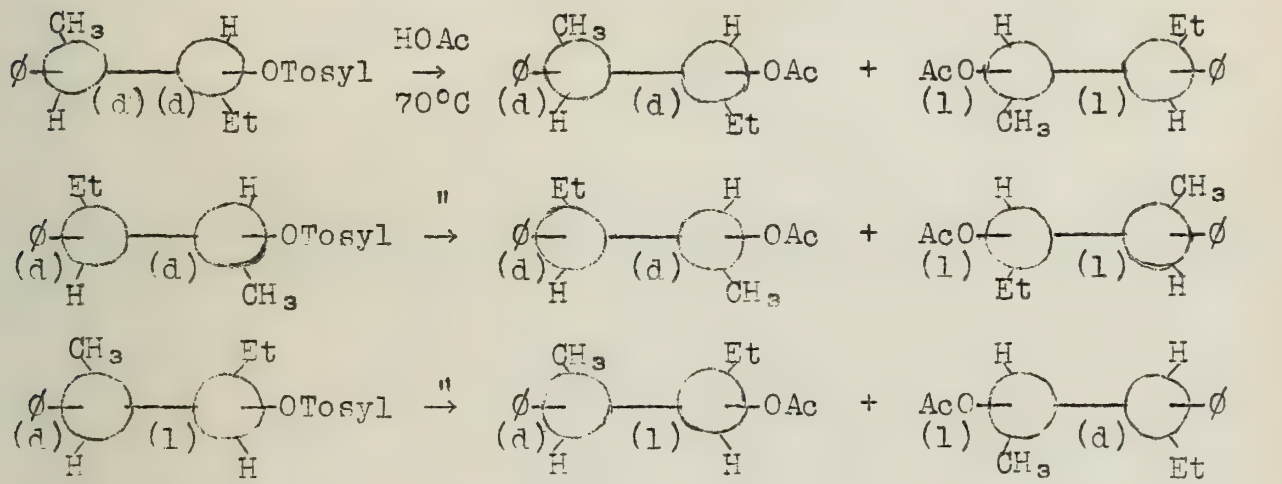
Experimental Results (1): Heating the p-toluenesulfonates of racemic and optically active acyclic alcohols at 70°C in glacial HOAc and qualitative and quantitative analysis of the product mixtures yielded the following results.

rac.-3-phenyl-2-pentanol →

rac.-3-phenyl-2-pentanol(70%) + rac.-2-phenyl-3-pentanol30%

rac.-2-phenyl-3-pentanol →

rac.-3-phenyl-2-pentanol(70%) + rac.-2-phenyl-3-pentanol30%



Conclusion: With the compounds studied, acetolysis led to a mixture of two acetates. One of these was always sterically identical to the starting material. The other acetate possessed the structure expected from a W. M. rearrangement in which the phenyl group migrated and both asymmetric carbon atoms underwent inversion. Therefore a true, stable, cyclic carbonium ion intermediate must have been formed.

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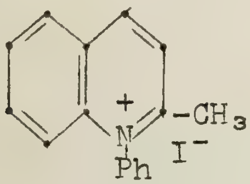
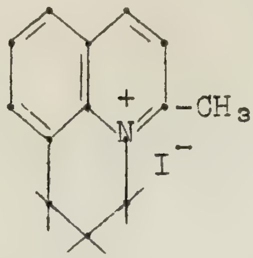
NEW QUINOLINE DERIVATIVES

Reported by Sheldon S. Simon May 19, 1950

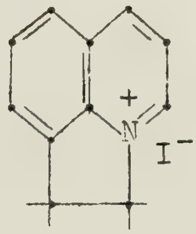
The alkyl quaternary salts such as I, unknown until now (1), and those of type II and III have been investigated by researchers at Eastman Kodak Company. The usual method of preparation by heating the base with the appropriate alkyl iodide, p-toluenesulfonate or the like was not applicable.



I

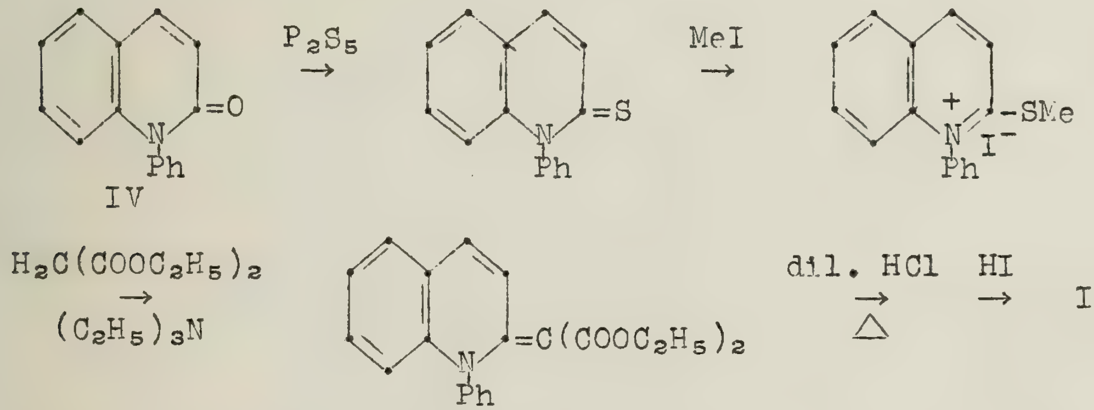


II

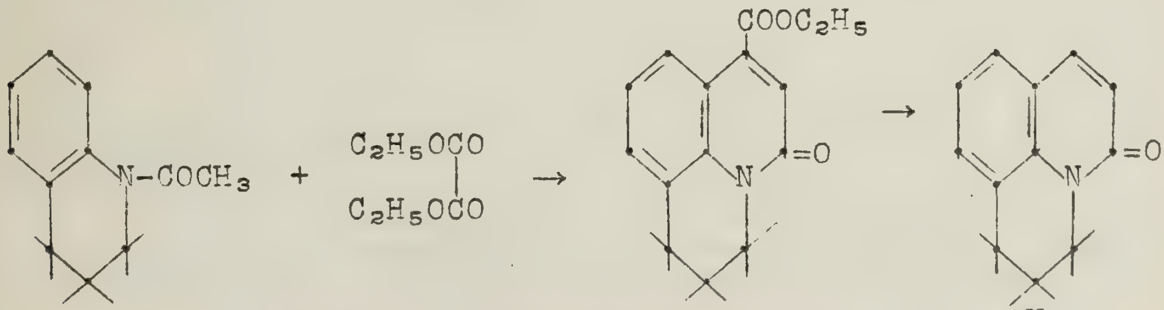


III

From 1-phenyl-2-quinolone, (IV), (available by several methods (2,3)) I was prepared by the following steps:



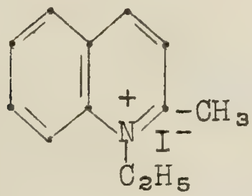
Salt II was prepared by a similar series of steps from compound V which was the result of using tetrahydroquinoline as the starting material.



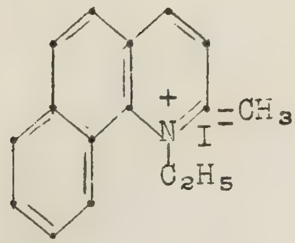
V

Using indoline in place of tetrahydroquinoline in the above sequence of reactions, the quinolone was obtained from which the salt III could be prepared in a similar fashion to II.

An attempt to prepare quinaldinium salts of type VI and VII



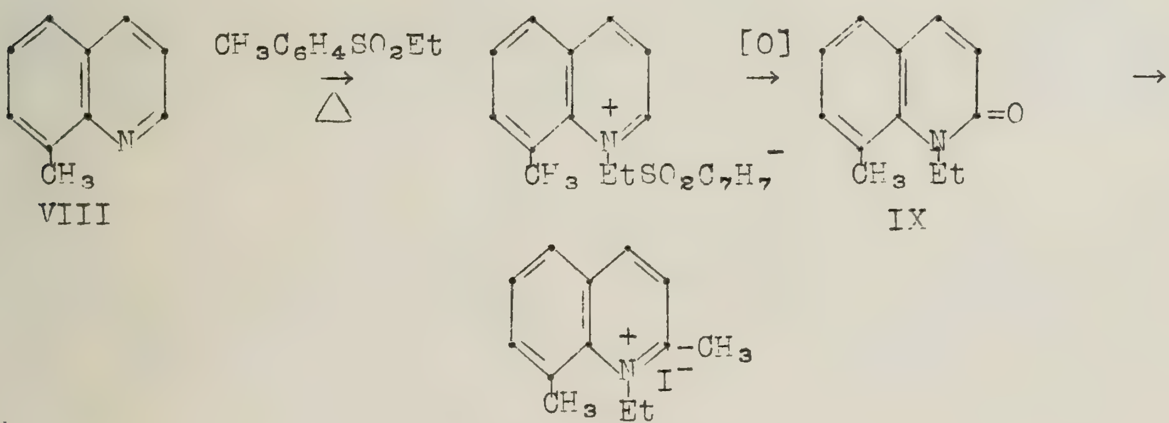
VI



VII

by quaternization of 8-methylquinaldine and 7,8 benzoquinaldine as a result of heating with ethyl iodide or ethyl p-toluenesulfonate proved to be unsatisfactory due to shielding of the nitrogen atom by adjacent groupings.

The starting point for the present synthesis of the desired product, (VII), is 8-methylquinoline (VIII) which is easily quaternized by heating with ethyl p-toluenesulfonate. The resulting salt is oxidized to the quinolone IX in the usual manner and from IX, VI is reached by a procedure similar to that shown for I.



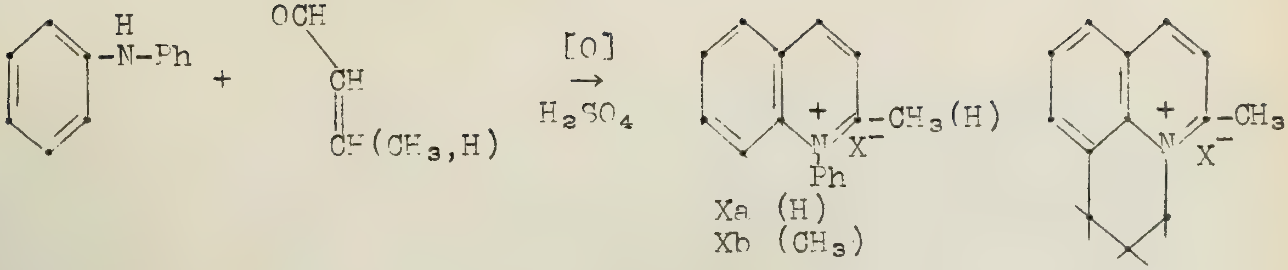
VIII IX VI

The same method was employed for VII, starting with 7,8-benzoquinoline.

Quinolinium and quinaldinium salts can be prepared (4) by a direct synthesis from secondary amines by condensing with acrolein and crotonaldehyde.

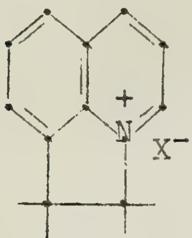
The hitherto unknow 1-phenylquinolinium salt, (Xa) is formed by a newly developed extension of the Skraup synthesis. Diphenylamine hydrosulfate is treated in nitrobenzene with acrolein and the derived salt is isolated as the perchlorate in yields of 10%.

The quinaldinium salts XI and XII were prepared in a similar fashion using crotonaldehyde, starting with diphenylamine, tetrahydroquinoline and indoline respectively.



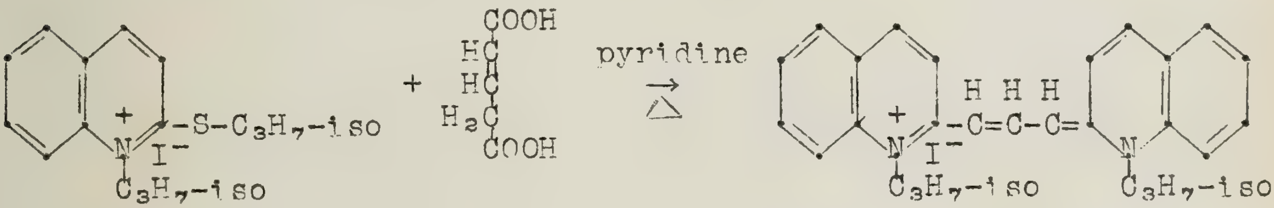
Xa (H)
Xb (CH_3)

XI



XII

Related to the quinolines are the cyanine dyes which are potential photographic sensitizers. Brooker, Heseltine and coworkers (5) have prepared cyanines containing the N-isopropyl group by a method more promising than that of Heilbron (6). When 1-isopropyl-2-isopropylthioquinolinium iodide (XIII) was condensed with glutaconic acid by Kendall's method (7), 1,1'-diisopropyl 2,2'-carbocyanine iodide, (XIV), was formed. This is the only example in literature of a cyanine containing an isopropyl group attached to a nitrogen atom.



XIII XIV

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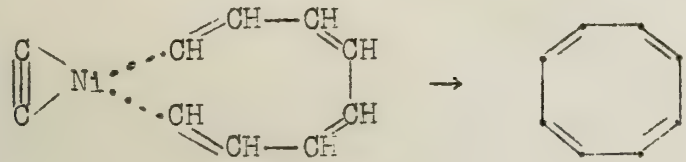
CYCLOOCTATETRAENE

Reported by Charles J. Strickler May 19, 1950

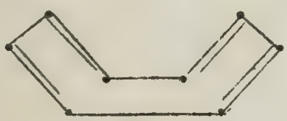
In 1948 Reppe and co-workers (1) reported a new method for the preparation of cycloöctatetraene and extensive studies of its reactions and derivatives. Heretofore COT was known only through the long and laborious Willstätter synthesis from Pseudopelletierine (2). The Reppe synthesis was accomplished by cyclic polymerization under pressure of acetylene with tetrahydrofuran as solvent and a divalent nickel salt, such as $Ni(CN)_2$, as the catalyst. This discovery was undoubtedly very important to Germany as COT can be readily isomerized to styrene. Reppe postulates the actual catalyst as being nickel acetylide which coordinates the ends of an acetylene tetramer and thus directs the cyclization.



golden-yellow liquid
B.P. - 142-3°C/760 mm.
M.P. - 7.0°C

70-90%

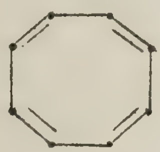
COT's double bonds have been shown to be olefinic in nature both by chemical studies and physical measurements. It is oxidized by standing in air, adds halogens readily, and undergoes the Diels-Alder reaction with the formation of characteristic adducts. There are at least four conceivable spacial structures, but the present information indicates either form I (3) or II (4).



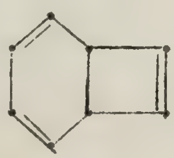
I. "Tub" (all cis)

II. "Crown" (all trans)

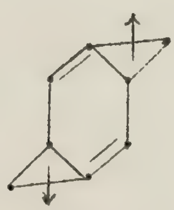
During the studies of the derivatives it was observed that they fell into three distinct classifications. Reppe attempted to explain this by assuming that COT can react as if present in any one of the three following forms.



I. Eight-membered ring



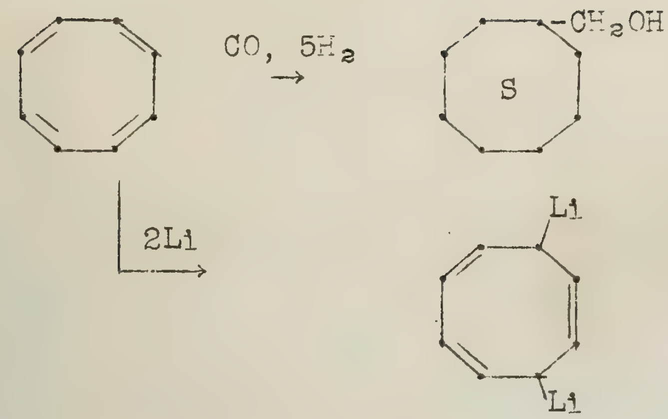
II. Bicyclo(0,2,4)-octatriene(2,4,7)



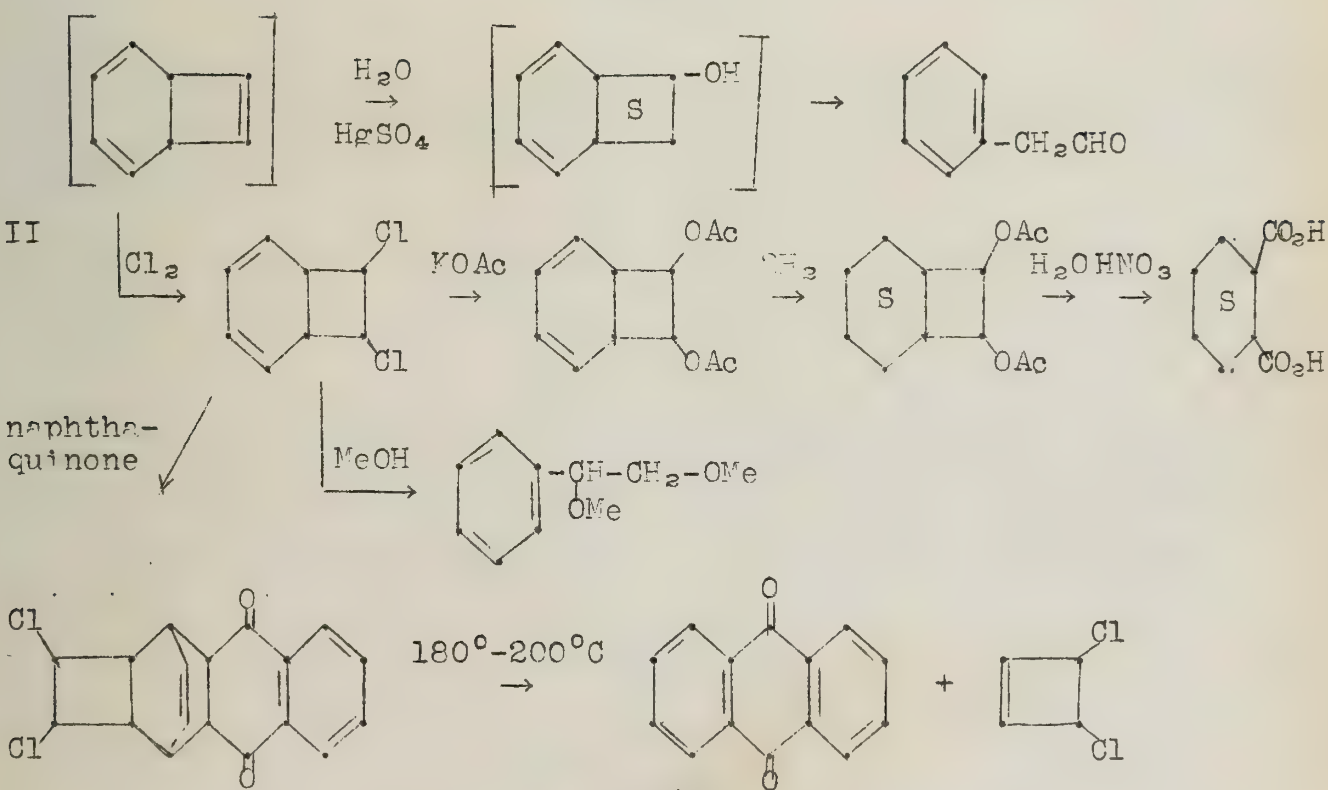
III. 1,2-4,5-Dimethylenecyclohexadiene-2,5

As examples:

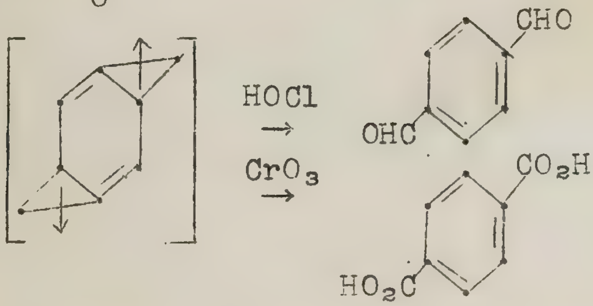
I



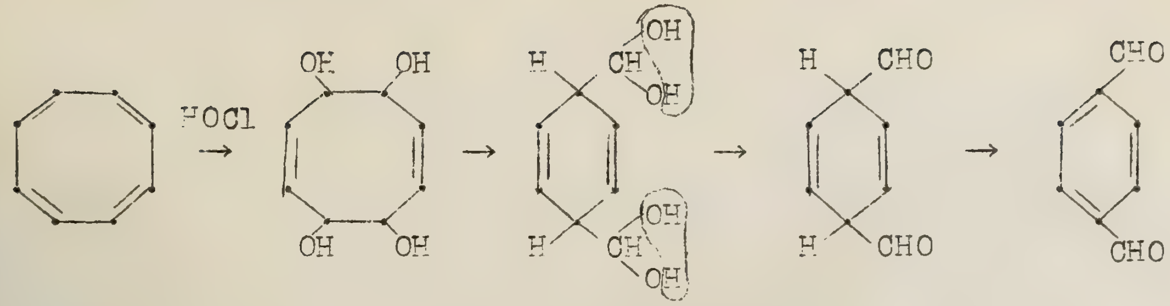
II



III

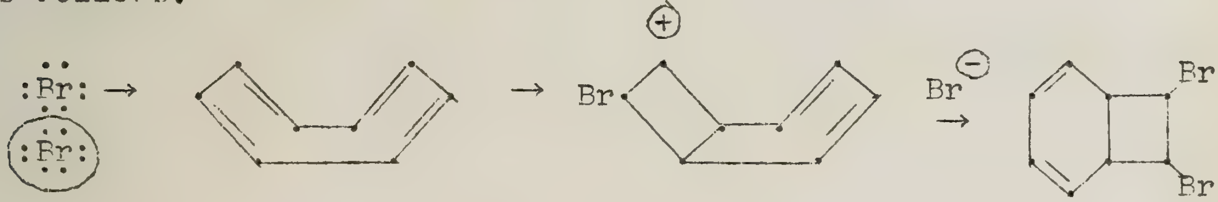


The reactions in class I are the expected, and those in class III were logically explained by Professor Schopf, of Darmstadt, in the following manner.



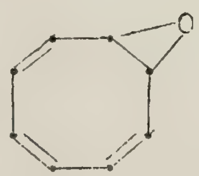
The majority of the derivatives fall into class II. Reppe used formula II as if it existed prior to reaction to explain the products formed. This concept explained the products well save for the case of the two isomeric dimers formed as a result of COT undergoing a Diels-Alder reaction with itself. One isomer contained two double bonds and the other, three. Reppe's type II gives two possibilities for the isomer containing two double bonds and none for the one containing three.

However, later ideas by Friess and Boekelheide (5) using the "tub" form and the principle of "participation by neighboring bonds" as advocated by Winstein and Adams (6) explain the type II reaction as follows.



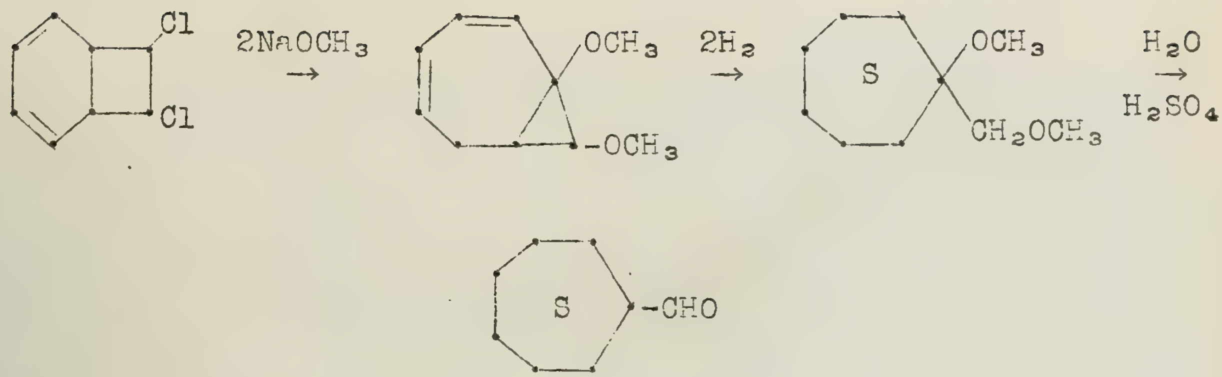
Upon applying this mechanism to the dimerization reaction one obtains one structure containing three double bonds and one containing two; this agrees very well with the experimental results.

Reppe postulated the structure of the oxide formed by the action of peracids upon COT as:



Friess and Boekelheide, on the other hand, favor the class II structure. They base their argument on the facts that the ultraviolet absorption spectrum compares well with that of cyclopentadiene and that the adduct with maleic anhydride contains but one carbon to carbon double bond while Reppe's structure should give two.

One seven-membered ring can be formed from COT.



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RECENT ADVANCES IN THE CHEMISTRY OF SUBSTITUTED ACETYLENES

Reported by John C. Wright May 19, 1950

I. The Conversion of Monosubstituted Acetylenes into Aldehydes: It is well known that under the influence of a peroxide, thiols undergo abnormal reactions with olefins (1), but little work has been done on the abnormal addition of such compounds to substituted acetylenes. Last year in trial experiments along this line, using hex-1-yne and a variety of thiols, the best results were obtained with the use of thiolacetic acid (2). The presence of peroxide was not necessary, although it was desirable. Products were isolated corresponding to the addition of either one or two moles of the sulfur compound. Treatment of the mono-adduct with semicarbazide acetate gave the semicarbazone of n-hexoic aldehyde. Hitherto hydration reactions of monosubstituted acetylenes have invariably led to the formation of methyl ketones.

$$RC\equiv CH \xrightarrow{HS\overset{O}{C}CH_3} RCH=CHS\overset{O}{C}CH_3 \xrightarrow{H_2N\overset{O}{C}NHNH_2} [RCH=CHSH] + CH_3\overset{O}{C}NHNH\overset{O}{C}NH_2$$

$$\xrightarrow{H_2N\overset{O}{C}NHNH_2} H_2S + RCH_2\overset{H}{C}=N\overset{H}{N}\overset{O}{C}NH_2 \quad (60\%\ R = C_4H_9)$$

Replacement of the semicarbazide by 2,4-dinitrophenylhydrazine resulted in formation of the 2,4-dinitrophenylhydrazone of n-hexoic aldehyde.

Phenylacetylene ($R = C_6H_5$) and p-methoxyphenylacetylene ($R = p\text{-}CH_3OC_6H_4$) underwent this reaction to give monothiolacetates in yields of 70% and 75% respectively. These compounds were converted to their corresponding semicarbazones in yields of approximately 50%.

Attempts were made to obtain unsaturated aldehydes via the addition of thiolacetic acid to vinyl acetylene ($CH_2=CHC\equiv CH$). However mixutres of adducts which could not be separated were obtained. Unsaturated aldehydes were prepared using ethynyl carbinols.

$$(CH_3)_2\overset{OH}{C}-C\equiv CH \xrightarrow{HS\overset{O}{C}CH_3} (CH_3)_2\overset{\overset{H}{O}}{C}CH=\overset{H}{C}S\overset{O}{C}CH_3 \rightarrow (CH_3)_2C=CH\overset{H}{C}=O$$

The results of this work are to be published later.

When the product resulting from the addition of two molecules of thiolacetic acid to one of hex-1-yne was treated with the usual carbonyl reagents no evolution of H_2S was detected. Also, no crystalline derivatives such as would be expected from a 1,1 addition product (fig. I) were formed. Hydrolysis however gave hexane-1,2-dithiol. Thus the diadduct was formulated as hexane-1,2-dithioldiacetate (fig. II). This is in accord with results obtained by Young et. al. (4), who prepared 1-bromohexene and 1,2-dibromohexane by the peroxide catalyzed addition of HBr to hex-1-yne.

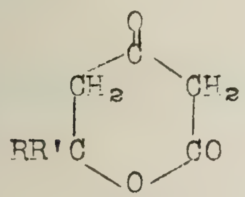
I $C_4H_9CH_2CH(S\overset{\overset{O}{\|}}{C}CH_3)_2$ II $C_4H_9\overset{S\overset{\overset{O}{\|}}{C}CH_3}{CH}CH_2S\overset{\overset{O}{\|}}{C}CH_3$

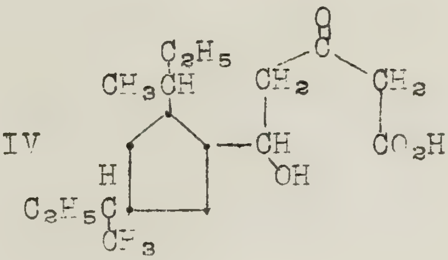
II.. <u>Reformatsky Reactions with Propargyl Bromides</u>: Recently it has been shown (3) that propargyl bromide, in the presence of zinc, reacts with a variety of carbonyl compounds to give the corresponding carbinols in good yields.

$$R\overset{\overset{O}{\|}}{C}R' + BrCH_2C{\equiv}CH \xrightarrow{Zn} HO\underset{R'}{\overset{R}{C}}CH_2C{\equiv}CH \quad \begin{array}{l}(R = \text{aryl, alkyl or H})\\(R' = \text{aryl or alkyl})\end{array}$$

This is an improvement over the former synthesis of such alcohols using sodium acetylide and 1,2-epoxides. Many of the epoxides necessary for preparing more complex compounds are inaccessible.

This reaction is of significance because the hydroxy acetylenes thus formed can be converted into 4-hydroxy-5,6-dihydro-2-pyrones (fig. III). These pyrones possess structures similar to the lactone of auxin-b (fig. IV), a plant hormone of importance for growth control.

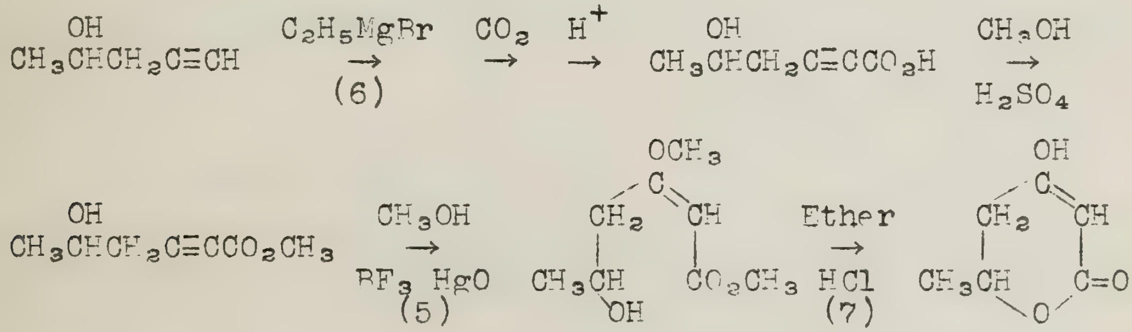
III 

IV 

(R = aryl, alkyl or H)

(R' = aryl or alkyl)

The general procedure used in these studies for the preparation of auxin-b type compounds is:



This Reformatsky type reaction has been found to proceed equally well with the substituted propargyl bromides: 1-bromohept-2-yne ($CH_3(CH_2)_3C{\equiv}CCH_2Br$) and the secondary bromide 3-bromohex-1-yne ($CH_3(CH_2)_2CHBrC{\equiv}CH$).

III. <u>The Preparation of α,β-Acetylenic-γ-Ketoesters</u>: A convenient route to acetylenic ketones was published in 1946 (8). The procedure involves oxidation of the corresponding secondary alcohol using chromic acid, preferably in acetone.

$$\underset{\mathrm{OH}}{\mathrm{RCHC{\equiv}CH}} \rightarrow \underset{40\text{-}80\%}{\mathrm{R\overset{}{\underset{\|}{C}}C{\equiv}CH}} \quad (\mathrm{R} = \mathrm{C_6H_5},\ \mathrm{CH_3\overset{H}{C}{=}\overset{H}{C}},\ \mathrm{C_3H_7},\ \mathrm{CH_3})$$

Recently this technique has been applied to α,β-acetylenic-γ-hydroxy acids and their esters (9). The results of this work are as follows:

A. Oxidation of the esters:

$$\mathrm{R\overset{OH}{C}HC{\equiv}CCO_2CH_3} \xrightarrow[\text{acetone}]{\mathrm{CrO_3}} \mathrm{R\overset{O}{\overset{\|}{C}}C{\equiv}CCO_2CH_3} \quad (\mathrm{R} - \mathrm{C_6H_5},\ \mathrm{C_3H_7},\ \text{and}\ \mathrm{CH_3})$$

Hydrolysis of the γ-ketoester resulted in the formation of an acyl pyruvic acid.

$$\mathrm{C_6H_5\overset{O}{\overset{\|}{C}}C{\equiv}CCO_2CH_3} \xrightarrow[\mathrm{KOH\ H_2O}]{\mathrm{CH_3OH}} [\mathrm{C_6H_5\overset{O}{\overset{\|}{C}}CH{=}\overset{OH}{C}CO_2CH_3}] \rightarrow \mathrm{C_6H_5\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CO_2H}$$

B. Oxidation of the acids: This oxidation was accompanied by hydration of the triple bond to give the β,γ-diketoacid.

$$\mathrm{C_6H_5CH(OH)C{\equiv}C{-}CO_2H} \xrightarrow[\text{acetone}]{\mathrm{CrO_3}} \mathrm{C_6H_5\overset{O}{\overset{\|}{C}}{-}\overset{OH}{C}{=}CH{-}CO_2H} \quad 40\%$$

Treatment of the γ-ketoesters with amines resulted in 1,4 addition across the ketogroup. This is proven by hydrolysis of the adduct to give an acyl pyruvic acid.

$$\mathrm{C_6H_5\overset{O}{\overset{\|}{C}}{-}C{\equiv}C{-}CO_2CH_3} \xrightarrow{\mathrm{C_6H_5NH_2}} \mathrm{C_6H_5\overset{O}{\overset{\|}{C}}{-}CH{=}\underset{\underset{\displaystyle C_6H_5}{|}}{\underset{NH}{C}}{-}CO_2CH_3} \xrightarrow[\mathrm{OH^-}]{\mathrm{H_2O}}$$

$$\mathrm{C_6H_5\overset{O}{\overset{\|}{C}}{-}CH{=}C(NHC_6H_5)CO_2H} \xrightarrow{\mathrm{H_3O^+}} \mathrm{C_6H_5\overset{O}{\overset{\|}{C}}{-}CH_2{-}\overset{O}{\overset{\|}{C}}CO_2H}$$

IV. <u>The Reaction Between Nickel Carbonyl and Monosubstituted Acetylenic Compounds</u>: Treatment of a monosubstituted acetylene in a mixture of ethanol and HCl with a solution of nickel carbonyl in ethanol results in the formation of a substituted acrylic acid ester (10).

$$\mathrm{4RC{\equiv}CH + Ni(CO)_4 + 4C_2H_5OH + 2HCl} \rightarrow \mathrm{4R\underset{CO_2C_2H_5}{C}{=}CH_2 + NiCl_2 + H_2} \quad 50\%$$

$$(\mathrm{R} = \mathrm{C_4H_9})$$

Use of the acetates of secondary carbinyl alcohols ($RCH(OCOCH_3)C{\equiv}CH$) in this reaction gave good yields of the corresponding acrylic ester. However free secondary alcohols, tertiary alcohols ($R_2C(OH)C{\equiv}CH$), or acetates of the tertiary alcohols gave poor yields.

Application of the reaction to β,γ-acetylenic carbinols (fig. V) gave α-methylene-γ-lactones (fig. VI).

(R = H or CH_3)

V VI

Compound VI (R=H) has been obtained by the hydrolysis of a presumably glycosidic precursor occurring in Erythroniun Americanium (11), and found to exhibit weak antibacterial properties. More complex substances containing the α-methylene butyrolactone grouping have been isolated from natural sources (12,13,14), but no previous synthesis of this type of compound has been reported.

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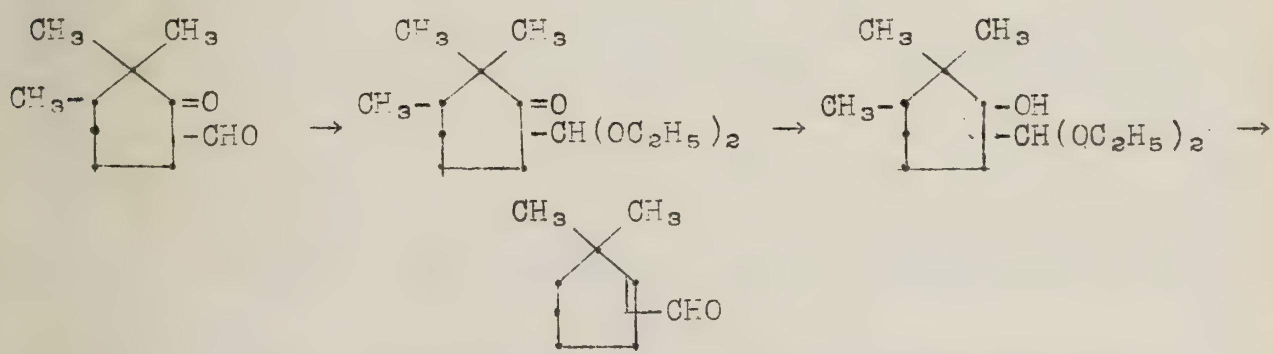
ACETALS AND KETALS AS BLOCKING AGENTS

Reported by Owen York, Jr. May 19, 1950

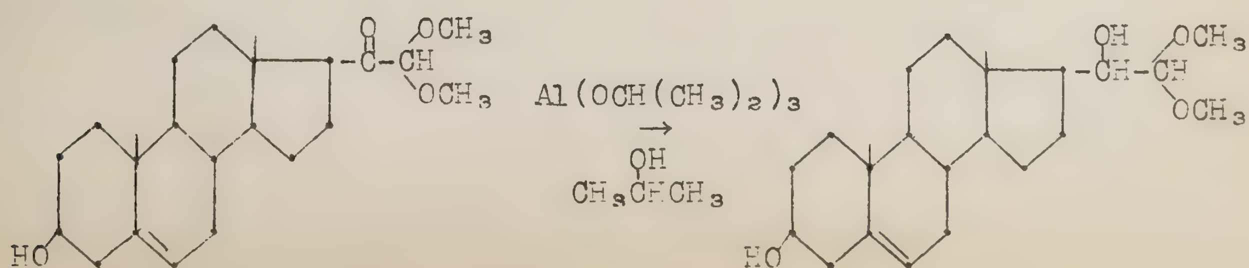
Introduction: Acetals and Ketals have been known for many years, but have been put to very little use in synthetic chemistry. In this respect, they offer possibilities as agents for blocking of carbonyl groups in order that other functions may be treated in various ways. The reaction of carbonyls with alcohols often proceed with difficulties and the products are even more often unstable, especially in the case of ketones. In order to overcome these difficulties, cyclic acetals and ketals have been used.

Salmi (1) devised a simple process for preparation of cyclic ketals. The ketone is mixed with slight excess of ethylene glycol in benzene solution and a small amount of p-toluenesulfonic acid is added. This is refluxed and the water formed is removed by azeotropic distillation with the solvent. Yields were good, acetoacetic ester giving 87% of the ethyleneketal. Kuhn (2) studied the same preparations and found that sulfuric or benzenesulfonic acid could be substituted for p-toluenesulfonic acid and comparable yields were obtained.

One of the most studied reactions of these compounds is reduction by the Bouveault-Blanc method. A few examples of carbonyl blocking by simple acetals have been utilized in the past in reduction reactions. Fischer (3) in 1898 converted cinnamaldehyde to benzylacetaldehyde by reduction with sodium and ethanol after first protecting the aldehyde group by forming the diethyl acetal. Wohl and Lange (4) reduced methyl glyoxal to α hydroxy propionaldehyde. Ruzicka et. al. (5) was working in the irone series and brought about the following transformation.

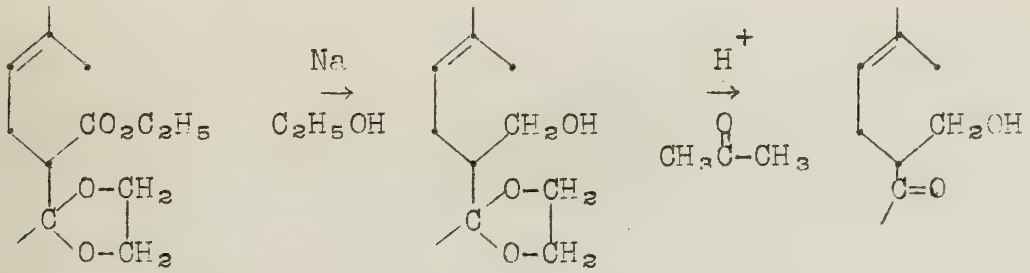


Schindler et. al. (6) used methyl acetal as a blocking agent in the sterol field. e.g.



After cleavage of the acetal and conversion to the acetate an overall yield of 68% was obtained.

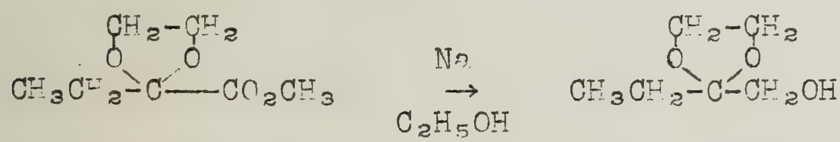
Schinz and Schappi (7) in their synthesis of dl-lavandulol carried out the following conversion:



This is principally the type of work done with acetals in the past.

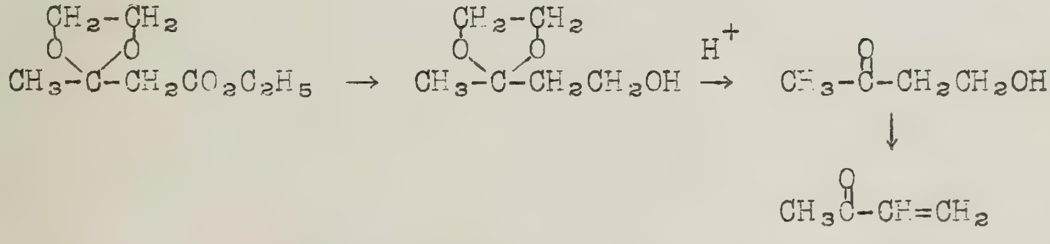
Some recent work as been applied to the ketalesters in particular (8).

The α-Ketalesters -

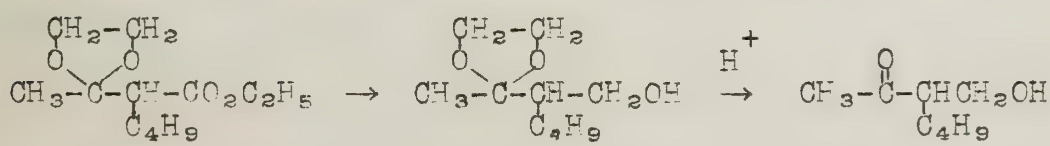


This holds little interest.

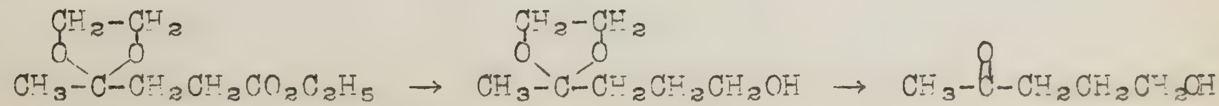
The β-Ketalesters -



Some α-alkyl substituted acetoacetic esters were studied, e.g.



The γ-Ketalesters -



This particular example is not practical because of the difficulty of separating the ketoalcohol from ethylene glycol due to

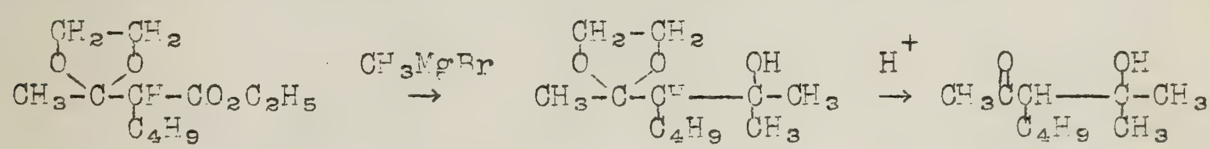
similarity of boiling points. It has been suggested, however, that it could be applied to higher homologues.

All the reductions indicated were carried out in boiling ethanol using 2-2 1/2 fold excess of sodium.

β-Ketalacids and their Chlorides: Some further applications of the β-ketal esters were made. The β-ketalacids and their chlorides were studied. It was known that the free β-ketoacids lose CO_2 at room temperature, but the ketalacids were found to be stable. Kuhn (2) had previously prepared α-dodecyl acetoacetic acid, but was unable to isolate the simple acetoacetic acid ketal. Williman et. al. (8) succeeded in preparing this ketal acetoacetic acid by saponifying the ketal ester with alcoholic sodium hydroxide, evaporating the sodium salt to dryness, and taking the salt up in dilute hydrochloric acid. The acid (M.P. 30°) precipitated on standing in the cold solution. It could be distilled in a high vacuum with only slight decomposition. Carbon dioxide begins to be evolved at 110°C.

The ketal acylchloride is formed by suspending the sodium salt in benzene and treating it with thionyl chloride. Ethylene ketal-acetoacetyl chloride decomposes at room temperature, but is stable in ether or benzene up to 45°C. Such a solution can be used in reactions which are run below 45°C.

Reaction with Grignard Reagents: The reaction of β-ketal esters with Grignard reagents was studied. The resistance of acetals to attack by Grignard reagents was previously pointed out by Fischer (9) when he treated the semi-acetal of glyoxal with methyl magnesium iodide and obtained the acetal of α-hydroxy propionaldehyde. Williman et. al. (8) carried out the following reactions:

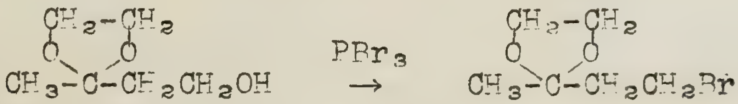


This keto alcohol was separated analytically pure by distillation.

Ethoxalation: The possibility of condensing ketal esters with oxalic ester was considered. Ethylene ketal of acetoacetic ester would not condense with sodium oxalic ester. A mixture of higher boiling oils was obtained but none of the oxalation product. The investigators theorized that this may be due to steric effects of the neighboring ketal residue. This was supported when they used levulinic ester ethylene ketal in the following manner:

The ethylene ketal of α-ethoxalyl-levulinic ester was obtained in a 40% yield.

<u>Formation of ketal halides</u>: The conversion of ketal alcohols to the corresponding ketalhalogen compounds was considered.



This reaction was carried out with success, giving good yields. The product, however, was not obtained analytically pure due to slight decomposition. Kuhn (2) had shown previously that direct ketal formation on the β-keto bromide would not go. The bromide ketal reacts with magnesium in ether solution, but the Grignard solution in presence of carbonyl compounds, such as acetone, did not give the expected carbinol, but rather a mixture of products which decomposed on distilling.

The stabilizing effect of cyclic ketals on compounds, such as acetoacetic ester, seems to offer several useful possibilities.

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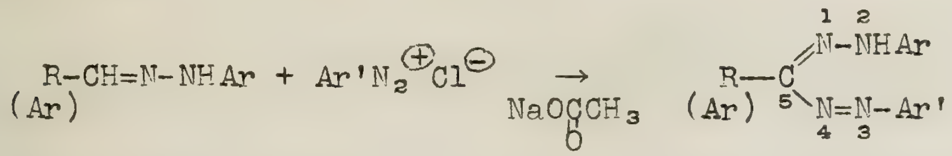
FORMAZANS AND TETRAZOLIUM SALTS

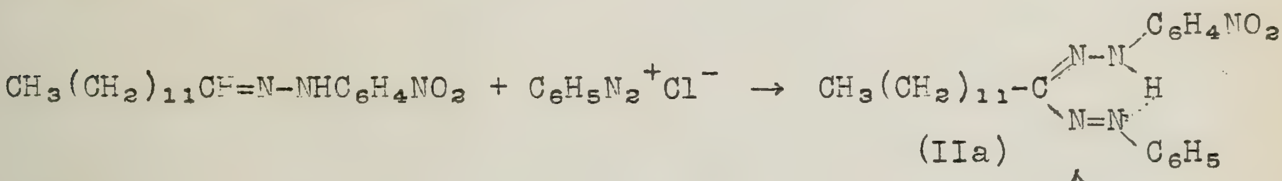
Reported by Rudolph F. Fischer May 26, 1950

Formazans: This type of compound, represented in general as (I), was first prepared in 1894 by von Pechmann (1). One of his methods, as modified by Bamberger (2), is of present preparative value; it involves the coupling of aryl diazonium salts with aryl hydrazones in buffered solution.

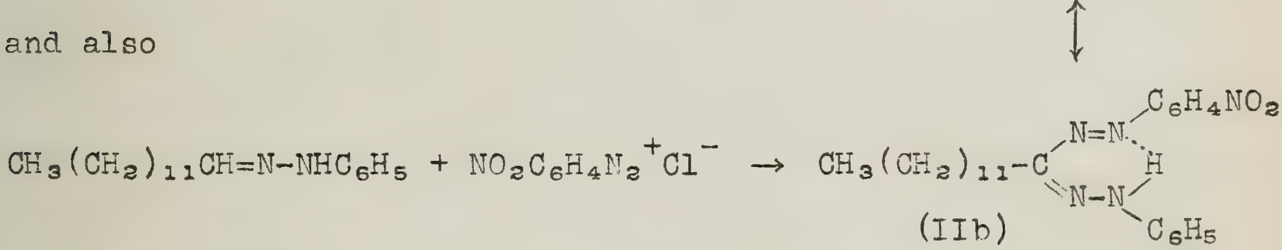


(I)

The active hydrogen in the formazans is in a position favorable for chelation, and it is found that when Ar and Ar' are different, the same product is obtained when they are interchanged in (I). Thus for example:

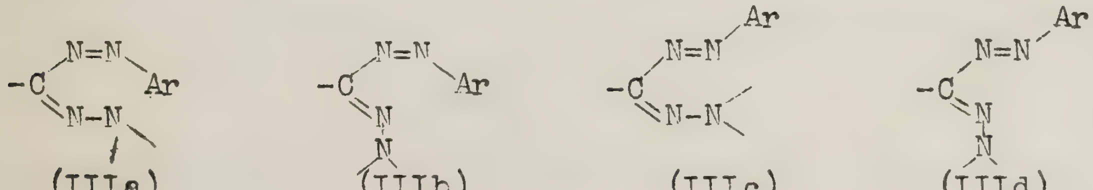


and also



It appears then that the formazans are best represented as resonating hybrids of type IIa ↔ IIb (3).

While four cis-trans isomers are theoretically possible about the two double bonds, (IIIa-d), the chelation might appear to confine the compounds to the "trans-cis" form (IIIc). However, consideration of Stuart models (3) shows that the "cis-cis" form (IIIa) is also capable of forming the intramolecular hydrogen bond.



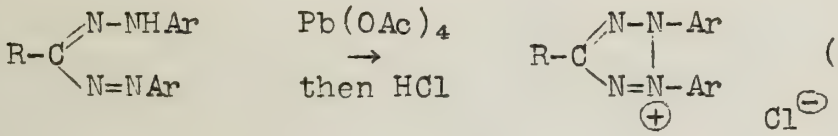
(IIIa) (cis-cis) (IIIb) (cis-trans) (IIIc) (trans-cis) (IIId) (trans-trans)

The formazans display a behavior typical of cis-trans isomers. They are brilliant red in the crystalline form and dissolved in non-polar solvents, but they tend to be yellow under the influence of brilliant visible light, especially in the more polar solvents.

On standing in the dark, the yellow form more or less rapidly reverts to the red; evidently the activation energies are relatively low. After determining that the yellow form is more stable when the group on the carbon atom is alkyl, Kuhn (3) succeeded in obtaining 2,3-diphenyl-5-ethyl formazan ("I", where R = Et, Ar = Ar' = C_6H_5) in two forms (one as orange needles, M.P. 102-3°, from methanol, and the other as red needles, M.P. 73-5°, from petroleum ether).

Formazans form resonating chelated complexes with bivalent metals (especially Cu^{++}, Co^{++}, and Ni^{++}), which can be used in purification (4).

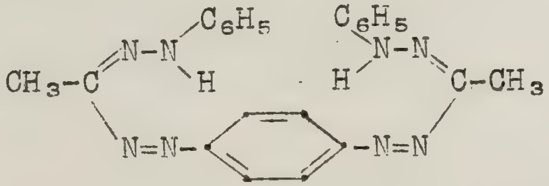
<u>Tetrazolium salts</u> (IV) are readily obtained by the action of certain oxidizing agents, notably lead tetraacetate, (5) on formazans. The yields average 80%.



(IV)

These salts are stable, colorless, and water soluble, and are easily reduced to the corresponding formazans. This rather unusual instance of the reduction of a colorless compound to a colored one is the basis for the recent interest in this field. It is found that living tissues are capable of effecting this reduction, while the corresponding dead tissues are not (6,7). Thus the salts may be used to determine the viability of seeds (8), or for biological staining (9), since the dye is precipitated in the cells of the organism. The compound (IV) in which R = Ar = C_6H_5, triphenyl tetrazolium chloride, is commercially available abroad, and also in this country (10) as "TPTZ".

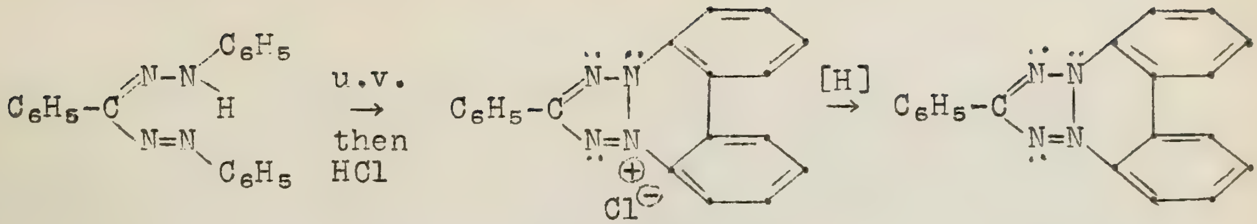
A serious disadvantage in animal biochemistry is the high toxicity of the formazans, and in a search for less toxic compounds of possible use in continued experiments with living animals, Jerchel (11) has synthesized a number of different types of diformazans and the corresponding di-tetrazolium salts. Of these,(V)



(V)

looks most promising; it is more highly colored and less soluble than the monoformazans.

Recently (12) it has been found that irradiation of triphenyl formazan in ethanol with ultraviolet light leads to a colorless salt with a deep blue fluorescence. This salt has been formulated as (VI). Reduction of (VI) does not give a formazan, but rather an unstable olive colored material, considered to be a type of free radical, (VII).



(VI) (VII)

If (VII) is treated with chlorine tetroxide (ClO_4), it gives a perchlorate salt identical with that obtained from treatment of the corresponding chloride (VI) with sodium perchlorate.

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ELECTROLYTIC FLUORINATION

Reported by H. Z. Friedlander May 26, 1950

Introduction. Although the standard fluorination procedures of direct action, replacement with metallic fluorides, and addition of HF to unsaturated compounds were improved vastly during the war (7, 14, 15), there is already a more promising process. This new method due to Simons is the electrolysis of HF solutions of organic compounds in a one compartment cell, a process which is safe and convenient since it does not use or produce dangerous F_2 either directly or indirectly. It is now being developed industriall.

Organic fluorocarbons are useful not only in theoretical studies but also as lubricants, resin monomers, heat transfer agents, turbine impellents, dielectric media, fire extinguishers, refrigerants, gun recoil fluids, and aids in the separation of uranium isotopes. Completely fluorinated acetic and butyric acids enable the synthetic chemist to make the whole gamut of organic compounds containing some fluorine atoms.

Older Synthetic Methods (6, 10). Since its isolation in 1886 (Moissar) F_2 gas has been often used in attempts to make fluorocarbons directly The gas is explosive, costly, hard to make and keep, and inefficient always producing HF. Though vapor phase, countercurrent liquid, inert solvent, and even solid phase reactions have been tried, no smooth, synthetic process was ever found.

In 1905, Moissan and Chavanne observed that substitution is not safe even in the cold, and that solid methane with liquid fluorine (-187°) exploded. Ruff and coworkers made the simple fluorocarbons and $(CF)_x$ from wood charcoal or graphite and F_2 gas. In 1936 Ruff and Giese reported this interesting reaction:

$$AgCN + F_2 \rightarrow CF_3NF_2 + C_2F_6 + (CNF_3)_2 + CF_3NO + FCONF_2$$

Bockemüller used CCl_2F_2 and CCl_4 solvents and found that propionic acid was fluorinated β and γ. This and other reactions have given evidence that F_2 is not the same as the other halogens in reaction mechanism. Bieglow et al developed a direct fluorination method of volatile liquids in the vapor phase. Simons and coworkers made all the simple fluorocarbons from fluorine and carbon powder with a mercury catalyst in 1937. Direct fluorination with AgF_2 catalyst was found preferable to the CoF_3 method for making perfluorinated lubricating oils (7).

Many metallic fluorides have been used to fluorinate hydrocarbons directly. Hg, Ag, and Sb were the prewar favorites. CoF_3 was used by the Johns Hopkins group (Fowler process - developed by DuPont); MnF_3 and CeF_4 are just as good.

A common route to fluorocarbons is the replacement of other halogens (7, 8, 15). The Purdue group made lubricants from hexachloroxylenes using SbXy and HF (developed by Hooker Electrical). KF, but not NaF, will cause the replacement of chlorine with fluorine in many functions. MnF_3, AgF_2, and CoF_3 convert UF_4 to the

volatile UF_6. The Schiemann reaction gives aryl fluorides from the stable ArN_2BF_4 (9).

HF has been added to acetylenes and olefins; the latter reaction is reversible. Some examples are:

$$CH_3CH = CCl_2 + HF \rightarrow CH_3CH_2CCl_2F$$
$$CH \equiv CH + HF \xrightarrow{\text{violent}} CH_2 = CHF + CH_3CHF_2$$

Anhydrous HF and alcohols form an equilibrium mixture of about 40% alkyl fluoride, but the separation is difficult and not generally useful. HF splits cyclopropane to give propyl fluoride.

The Electrolytic Process (1-5)

Simons and coworkers have developed a process for fluorinating many classes of organic compounds in a conducting solution of anhydrous HF. The gaseous lower fluorocarbons and fluoroform are collected with H_2 in large containers, separated and distilled. The heavy perfluoro compounds are drained from the bottom of the cell. At the voltages employed no F_2 is produced and fragmentation is minimised.

In an iron or copper cylinder, which serves as the cathode, the compound is dissolved in HF and the solution electrolysed for several days at 5 to 6 volts, current density 0.012 to 0.04 amperes /cm^2 with a nickel anode. The cylinder is cooled in an ice bath to prevent vaporization (HF boils at 19.4°C), and additional HF and solute are added periodically to maintain a constant level. The main products are perfluorocarbons of the same number of carbon atoms as the organic starting material. This method has been used to make CF_3COOH and C_3F_7COOH in pilot plant quantities by an undisclosed variation.

Hydrocarbons are not very soluble in liquid HF so a conductant such as H_2O, CH_3OH, CH_3COOH, or pyridine must be added. Typical results are:

$$\text{n-octane (41 g.)} + \text{HF (800 g.)} \xrightarrow[\text{40 g}]{CH_3COOH} C_8F_{18}\text{ (14.6 g.)}$$

$$\text{n-octane (40 g.)} + \text{HF (1200 g)} \xrightarrow[\text{38 g}]{CH_3OH} C_8F_{18}\text{ (35 g)}$$

$$\text{n-octane (160 g)} + \text{HF (1kg)} \xrightarrow[\text{70 g}]{H_2O} C_8F_{18}\text{ (70 g)} + C_2F_6\text{ (27 g)} + CF_4\text{ (54 g)}$$

At about 5.5 volts no F_2 is produced even momentarily since there is a large percentage of perfluoroöctane produced, no F_2 in the effluent gas stream, and no explosions. At higher voltage F_2 is found, explosions occur, and there is complete fragmentation.

Acids are decarboxylated in a Kolbe manner to give completely fluorinated products in these original experiments. Oxygen and

nitrogen atoms help HF solubility so no conductant is necessary.

$$C_4H_9CO_2H + HF \xrightarrow[135\ hrs.]{5V} \text{fluorocarbons } (C_4 + C_5) + CF_4,\ CF_3H,\ C_2F_6$$

5 moles 34 moles 377 g. 30 g.

Kilogram amounts of CF_4, fluoroform, and perfluoroethane have been made from acetic and propionic acids respectively.

<u>Alcohols</u> polymerize in HF to give fluorine containing polymers:

$$C_5H_{11}OH + HF \rightarrow \text{gases } CF_4,\ CF_3H,\ C_2F_6$$

8 moles 34 moles 75 g.
+ 260 g. liquid fluorocarbons
+ 260 g. polymer

The liquid was mostly C_5F_{12} and C_4F_{10}.

<u>Amines</u> give excellent results upon electrolysis:

$$\text{pyridine} + HF \xrightarrow[76\ hrs]{5.7\ volts} NF_3 + C_5F_{12}$$

0.66 moles 35 moles 68% (theory) 72% (theory)

In proceeding from acids through neutral alcohols to bases it has been found that fragmentation of the carbon chain decreases, yet in all these experiments the main products have the same number of carbon atoms as the starting materials.

There are five systems of nomenclature now used in describing fluorinated hydrocarbons. Partially fluorinated compounds can be designated by number or Greek letter, and compounds of carbon and fluorine only by "per", "ψ", or "forane."

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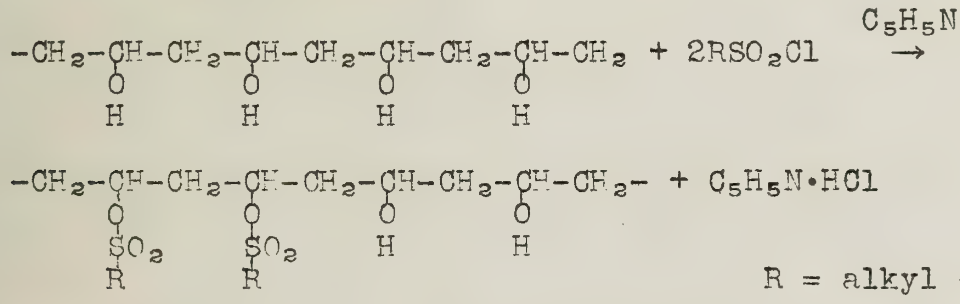
NEW PREPARATIONS AND REACTIONS OF SULFONIC ESTERS

Reported by Richard J. Hellmann May 26, 1950

The investigation of vinyl sulfonates has led, through work on polyvinyl sulfonates, to some very interesting non-polymer chemistry.

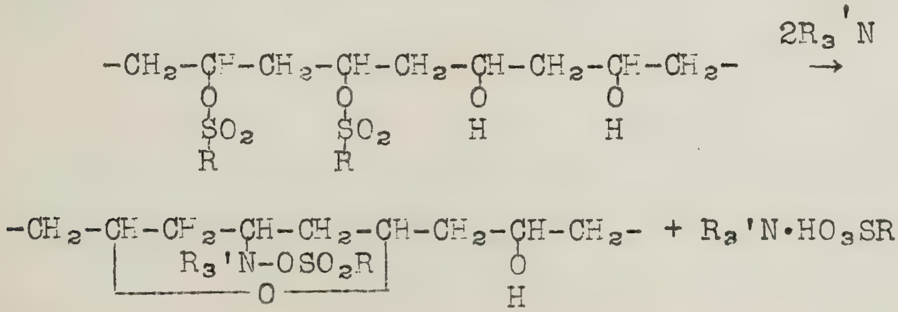
Since monomeric vinyl sulfonates are unknown, Reynolds and Kenyon decided to utilize polyvinyl sulfonates in their investigations (1). However, in order to do this, they first had to develop a method for preparing polyvinyl sulfonates. Only a small amount of work had been done previously along these lines by Izard and Morgan (2) whose method produced polymers containing a relatively low sulfonate content and an appreciable amount of vinyl chloride units. These results had also been observed in the sulfonation of sugar derivatives (3). They solved this problem by swelling polyvinyl alcohol, and then treating it with a sulfonyl chloride in the presence of a tertiary amine, preferably pyridine, below 10°. This procedure produced polyvinyl sulfonates of high vinyl sulfonate and negligible vinyl chloride content.



I

R = alkyl or aryl

Having obtained the polyvinyl sulfonates, they studied their reactions with amines. Two reactions occur when polyvinyl sulfonates are treated with tertiary amines (4): a. quaternization of vinyl sulfonate units with the tertiary amine, and b. an intramolecular condensation of vinyl sulfonate units with properly situated vinyl alcohol units to form cyclic ether units believed to be of the tetrahydropyran type. These two types of reactions are illustrated in II, however, this formula should not be construed as indicating the ratio or arrangement of these units.

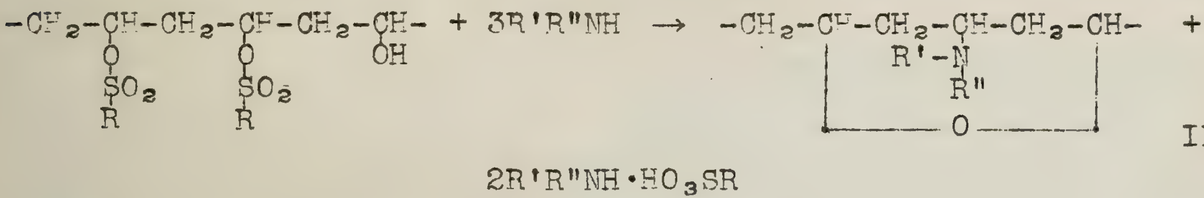


II

The two types of polymeric quaternary salts prepared previously contain pentavalent nitrogen atoms which are a part of the parent polymer structure (5,6). The quaternary salts formed by the action of tertiary amines on polyvinyl sulfonates differ from

the above in that the nitrogen atom is not an integral part of the original polymer molecule, and by the fact that they contain cyclic ether units.

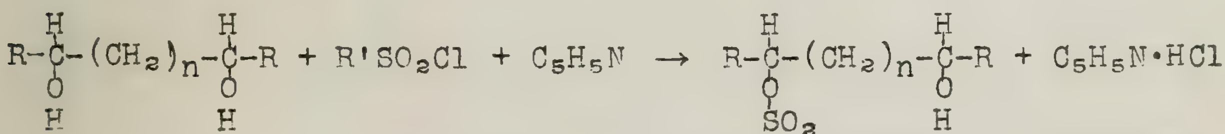
The reactions of the primary and secondary amines with polyvinyl sulfonates are somewhat different from those of tertiary amines (7). The two reactions that were found to take place are: a. the reaction of vinyl sulfonate units with the amine to yield N-substituted vinyl amine units, and b. the intramolecular reaction between a vinyl sulfonate unit and a vinyl alcohol unit to form a cyclic ether unit.



III

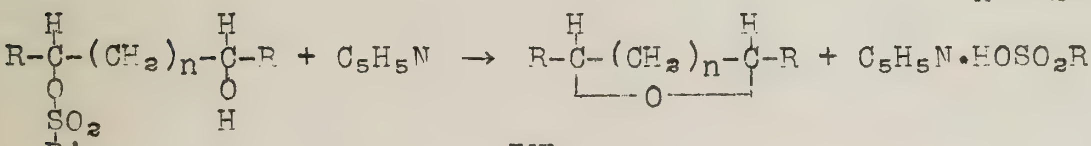
Only one other instance in polymer chemistry wherein a sulfonoxy group was replaced by an amino group has been recorded (8).

In order to elucidate the reactions leading to the formation of these cyclic ether structures, a study was made of the preparation of non-polymeric cyclic ethers of the tetrahydropyran and tetrahydrofuran types. During its course a method for the preparation of cyclic ethers was developed which involves the reaction of a glycol with one mole of a sulfonyl chloride in the presence of a suitable tertiary amine (9).



IVa

where R = H or CH_3
R' = CH_3, C_6H_5 or $CH_3C_6H_5$
n = 2 and 3



IVb

Control of conditions and choice of amine were found to be critical in these reactions. The conditions are important; for, if they are not controlled, the following side reactions (10) may occur to an extent sufficient to reduce greatly the yield of sulfonic ester in IVa: quaternization of the ester by the tertiary amine; replacement of the sulfonoxy group by the halogen from the amine hydrohalide; or splitting of the initially-formed ester into an unsaturate and a sulfonic acid. These side reactions can be controlled by preparing the sulfonic ester at temperatures below 10°.

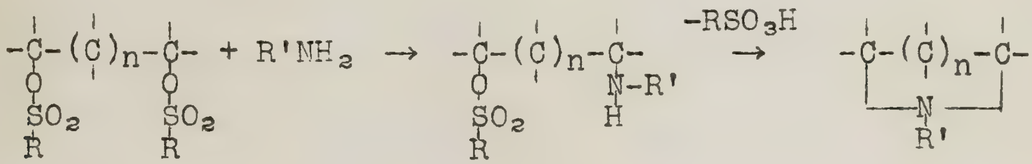
In the second step, IVb, the above side reactions may also take place, and the yields of cyclic ether will depend on the relative rates of the side reactions as compared to the desired reaction. These rates, in turn, will be determined by the nature of the sulfonoxy group, i.e., whether it is primary or secondary ($R = H$ or CH_3), by the nature of the organic base, by the particular sulfonic ester used and by the size of the cyclic ether ring to be formed, i.e., $n = 1, 2,$ or 3.

The formation of a five-membered heterocyclic ring of the furan series proceeds readily, the side reactions are not significant, and good yields are obtained.

However, in the formation of a six-membered tetrahydropyran ring the quaternization side reaction assumes great import, and amine bases with a low rate of quaternization must be chosen. In this regard 2,6-lutidine was found to be much more effective than pyridine. Other experiments have shown that 2,6-lutidine quaternizes simple sulfonic esters much more slowly than does pyridine.

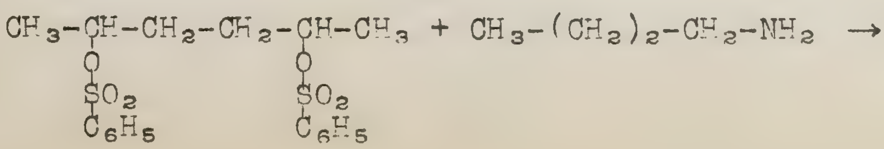
When the formation of a four-membered cyclic ether was attempted it was found that only unsaturated compounds could be obtained. This "side reaction" being so great in this case that no four-membered cyclic ether could be isolated.

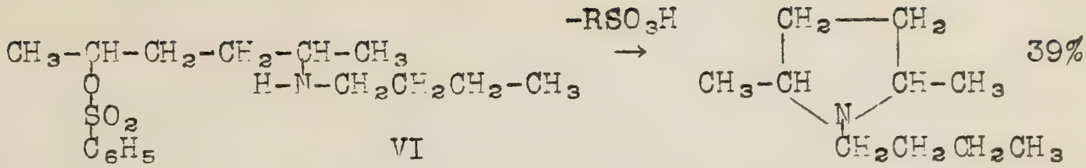
From the studies on the reactions of sulfonic esters, two methods were also evolved for the preparation of cyclic tertiary amines (11). The first of these is partial amination of a glycol disulfonate, followed by cyclization. As mentioned previously, it had been found that cyclic ethers with five- and six-membered rings could be prepared in good yields by the intramolecular reaction of a sulfonoxyl group with a properly located hydroxyl group. Analogously, since alkyl sulfonates react with primary amines to yield the corresponding alkylated amine, cyclic amines should result by the intramolecular reaction of a sulfonoxyl group with the hydrogen of a properly situated amine group.



V

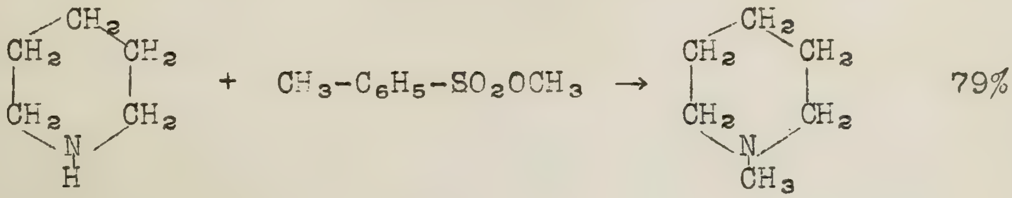
Good yields of the desired amines are obtained under experimental conditions which allow the reaction to take place stepwise as shown. One specific example is indicated in VI.





VI

The second method is alkylation, by an alkyl sulfonate, of a cyclic secondary amine. Although alkyl sulfonates are known to be excellent alkylating agents for primary and secondary amines, no previous description of the alkylation of cyclic secondary amines which utilizes this fact has been found in the literature.



VII

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